Archives of Neurology and Psychiatry

VOLUME 42 AUGUST 1939 NUMBER 2

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RECOVERY FROM APHASIA

STUDIED IN CASES OF LOBECTOMY

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When the first case of major (left) temporal lobectomy was reported by Fox and German [1] with an accurate study of the aphasic manifestations, the general impression among students of aphasia was that the case must have been extremely unusual and that the patient must have had remarkable capacity for compensation after loss of the lobe. The subsequent report of a case in which operation was performed by one of us (R.) showed that either the first impression was erroneous or that, by a peculiar coincidence, the second patient to be so treated was, like the first, unusually endowed. We now have the privilege of reporting 2 other cases in which major (left) temporal lobectomy was performed surgically and an additional case in which it was performed by nature, together with a case of surgical minor (right) temporal lobectomy. The remarkable clinical similarity (almost identity) of the 3 cases of left temporal lobectomy here reported to the 2 already published places the clinical manifestations following lobectomy (i. e., the performance of the minor [right] temporal lobe) beyond the realm of chance and proves that a person without any left temporal lobe is in general far superior to one with a slightly damaged lobe still in situ. The case of right temporal lobectomy shows that the minor lobe may be of considerable use even during complete functional activity of the major lobe. In the following account the evidence is presented.

REPORT OF CASES

CASE 1.—*Left temporal lobectomy. After operation marked acoustic verbal agnosia, alexia and agraphia with the syndrome of exceedingly rapid fatigue of all functions of language. Retention of personality.*

R. R., an Italian building contractor aged 53, under the care of Dr. C. B. Courville, had a condition that was diagnosed as tumor of the left temporal lobe.

1. Fox, J. C., Jr., and German, W. J.: Observations Following Left (Dominant) Temporal Lobectomy: Report of Case, Arch. Neurol. & Psychiat. **33**:791-806 (April) 1935.

Because of changes in personality, one could not approach the patient with the problem of treatment, and the family delayed until the patient was in coma. One of us (R.) at this point removed the left temporal lobe for an infiltrating astrocytoma. The line of incision, as mapped by Dr. Courville, who watched the operation, is shown in figure 1. After operation, the other of us (N.) was granted permission to study the case.

Comprehension of Spoken Language.—Comprehension of spoken language was good for generalities for a short time. He was usually able to answer correctly about a dozen questions, after which he "broke" and suddenly comprehended nothing. The following conversation will demonstrate this.

"What is your name?"	"Ross."
"Ross what?" (hesitation)	"Ratania."
"Where do you live?"	"I can't tell you where I live because I don't know where I live."
"Where do you live?"	"In my own house."
"How old are you?"	"About 25." (Actually he was 53.)
"Have you got a son?"	"Yes."
"What is his name?"	"The biggest one?"
"Yes, the biggest one."	"The biggest son is Ross."
"Just like you?"	"Yes, Ross."
"Have you a son named George?"	"George Ratania."
"What is this? [a dollar bill]?"	"A woman." (paraphasia)
"What are these [a pair of glasses]?"	"They're all right."
"What is the name of it?"	The answer consisted of complete neologistic jargon, and after this he understood nothing.

On another day, after a nap, when the patient was feeling well, the following conversation took place:

"Stick out your tongue."	(He did so.)
"Close your eyes."	(He did so.)
"Put your finger on your nose."	(He put it into his mouth.)
"Put your finger on your ear."	(He stared blankly.)
"Raise your hand."	(He stuck out his tongue.)

On still another day the following conversation took place:

"What is your name?"	"Ross Ratania."
"Where do you live?"	"Los Angeles."
"What street do you live on?"	"You find out the way you live yourself. You ask my wife, that's all." He then threw up his hands in expression of helplessness.

After this he understood nothing. He cocked his ears and listened as though listening to a foreign language. He did no better in listening to his son speak in Italian than in English. (He was born in America.)

Spontaneous Speech.—In talking spontaneously he usually spoke a few short sentences nearly correctly or with slight paraphasia. If he attempted anything

long at first, or even a sentence of a few words after having talked for a minute, his speech became severely paraphasic. When asked: "How long have you been in this country?" he answered: "I'm in America all my life, all my life. I still live, but before I die I go. When I was a young fellow I join the army, before I join the army, and I joined the navy one day and made the American army under when. But I went to army my own record I was just make a sweat. When I left the old country I left everything here. The last time I leave my wife Catalina."

Reading.—When shown "A" he said "I can read it," but he did not. When shown "S" he read it correctly. When shown "5" he read it correctly, but when shown "8" he read "5-10." Then, when shown "7" and "4" he read both correctly. When shown "Signs of the Times," he read, "Ninyet nugut tus tus."

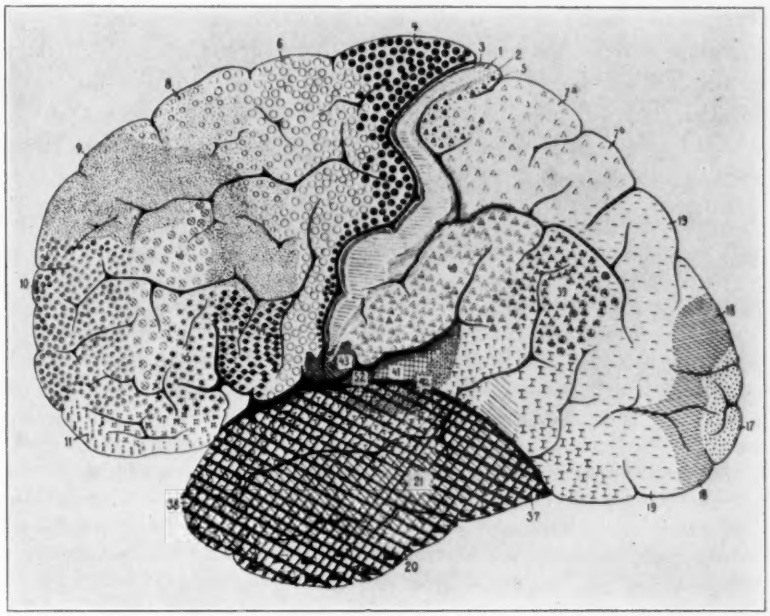

Fig. 1.—Diagram showing line of incision in case 1. The cross-hatched area represents the portion removed.

After a long rest he was shown "C," but could not read it. When shown "cat" he read Catherine." For "no breakfast" he read "new broker," and for "house" he read "careless."

To ascertain that the lack of ability to read was not merely paraphasia, i. e., inability to say what he meant, my co-workers and I prepared a series of words, such as "key," "safety pin," "red," "yellow," "green," "blue," "half dollar," "quarter," "pen" and "dime," and the corresponding colors and objects were provided for the patient to place on the appropriate words. He was shown several of them first. After a long time we gave up the attempt to teach him. He was totally unable to read (say) the words or to determine what they meant. He finally said: "No, no, my eyes. You know your business. I know my nation. I'm in no position to answer my nation." He had complete agnostic alexia.

Writing.—The patient had complete agraphia. He was unable to use a pencil at all, though he had had a fairly good education. (He had had agraphia before the operation.)

Calculation.—It was difficult to determine whether he was able to calculate. He gave the correct answer to "2 plus 3," but to similar problems he gave wrong answers. Of course, he had severe paraphasia, which prevented him from giving the correct answers orally, and he could not write them. Neither could he read.

No other form of agnosia was present. The patient was fairly well oriented, considering the circumstances. His change of personality had essentially disappeared as a result of the operation. He could not play cards, but had never been able to play.

Comment.—The case of this patient without a left temporal lobe corresponds exactly to the others already reported in the literature. The difference between his case and that of the others is one only of degree. He was not of as good material fundamentally and was not as well educated, that was all. It is worthy of note that the function in which the right side failed completely was that of writing, the most recently acquired and the most complex of all language functions.

CASE 2.—*Surgical removal of the anterior half of the left temporal lobe for cystic astrocytoma. Secondary hemorrhage into the posterior portion, with resultant hemianopia and aphasia. Recovery from the latter to a large extent. Residual alexia, agraphia and disturbance in calculation. Slowing in comprehension of spoken language. Stilted spontaneous speech. Retention of personality.*

J. E. M., a dentist aged 52, under the care of one of us (N.), underwent operation on Jan. 3, 1936, for cystic astrocytoma of the left temporal lobe. The growing portion of the tumor was attached mesially, and the surgeon (R.) considered it dangerous to attempt complete removal. After recovery from the anesthesia the patient talked fairly well and was in good condition except for weakness of the right arm and right side of the face for thirty-six hours. On the afternoon of the second day he became stuporous, and his temperature rose to 109 F. After this episode he was completely hemianopic, which he had not been before, and was unable to talk at all. By slow degrees he relearned to speak.

A record of the various stages is long and not particularly instructive. The patient taught himself to read, looking up words in the dictionary and practicing writing because he could no longer spell correctly. He worked so diligently at this reeducation that he showed signs of overwork. The examination here recorded was made after eighteen months.

Comprehension of Spoken Language.—The patient failed to grasp spoken language if it came to him a little rapidly. He listened as though trying to comprehend a foreign language; he cocked his ear when listening at all times, yet often had to ask to have conversation repeated. If speech came too fast the words were all jumbled to him.

"Tell me about the jerking of your limbs." "It's almost every day (we mustn't talk too loud; my wife . . .). The tongue doesn't move as often as it did." (The patient meant that the jacksonian jerking of the tongue had diminished.)

"What does move?" "Why, nothing in the mouth. It's cutting down on itself."

"Are you taking the tablets [phenobarbital]?" "Why yes, right up to date."

"How bad are the jerkings?" "Not nearly so bad as they were. They are cutting down."

"How long do they last?" "Oh, not enough to put me out, and they used to do that. They don't do that, so I think I'm ahead."

"Put your left index finger into your right ear." He hesitated a moment, smiled and did so.

"Hold up the index and little fingers of your left hand and the middle finger of your right." He asked to have the request repeated, then did correctly as requested.

Spontaneous Speech.—His speech was peculiarly stilted. This is shown by the following conversation.

"What do think of the administration?" "National or city?"

"National." "It's doing things of unusual . . . Roosevelt undoubtedly saved this country when he closed the banks. He undoubtedly is going into the expensive condition too deeply. To get into the billion dollars, something that is never happened to the world. Therefore, the good that he does is not sufficient to wipe out the bad that he does; I don't know whether that meets with your approval or not; I'm a Republican as far as that's concerned. Not that I want a Republican elected every time."

"What do you think of the strikes?" "Well, I think that there is a greater number every time there is a success in the nation. Success in the nation. No. I'll take that back. Every time there is a greater income. . . . You know I think faster than I can talk, and I may not talk like I think." (Consciousness of his paraphasia.)

"Why don't you?" "Because the vocabulary isn't there, and I find my forgetfulness comes upon myself before I can change. I don't want to say that either. I can't answer you."

"You are doing very well." "Well, I'm thinking just the right way according to I read, but I don't read as rapidly as I used to. But people are too impatient to let me talk slow. My wife and my family, my daughter wouldn't do it on a bet."

"Is it harder to read than to understand spoken language?" "Oh, yes . . . Bob and his mother don't get along."

"Why not?" "I don't know. It's real and not imagined, and it's possibly that thyroid of hers. Anyway, she ought to have more patience with him and with me."

"What irritates you most, quarreling?" "No, there isn't anything that irritates me, because when my wife enters with an argument on my son, I just walk out on it. So that's the reason I want to go away. I was there six weeks, and I only got back Saturday [from a sanatorium]. And I wouldn't have quit there if it hadn't been for the heat." (It had really become warm.)

"Do you do any writing?" "Oh, yes, I practice on it constantly. But I can't write fast as I used to. Nor spell. Oh my, whew! I'm learning all over again. See, I have the dictionary over there, and wherever I go I take it with me."

"Do you do any physical work?" "No."

"Is your hemianopia improving?" "No. They are just as bad as they ever were."

"Do you have any sensory loss anywhere?" "No, no, but I still have those manipulations here." (He indicated his right leg.)

"Do you mean jerkings?" "Yes, but I don't tell her [his wife]."

Calculation.—Considering the fact that the patient had been especially capable in mathematics, one must conclude from his performances in the following test that this function had been considerably affected by the operation. He was unable to solve the problem $\frac{21 \times 43 \times 20}{4 \times 22}$. He failed to observe that cancellation was possible, and even when this was suggested he did not know how to proceed. He finally multiplied as follows:

```
  43
  21
 ---
  43
 83
----
 873
  20
-----
17460
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Then he divided as follows:

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88 / 17460 / 219
   88
   --
   866
    6
    8
    2  12
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and then he surrendered. He correctly multiplied 3 by 4, but when asked about 7×9 he hesitated and said: "That's too far. Let's see. I can figure it out if you'll wait a minute—63, is that right?" When asked how he figured it out, he explained that he multiplied 7 by 3 three times. He correctly calculated 8×11, but with 9×9 he hesitated for some time, repeated "9×9" and said: "I can't even guess it. I give up." When asked whether he had been proficient at mathematics he replied: "I'll say; I'll come back at it."

Before his illness the patient had been a very good chess player. After the surgical procedure he was handicapped by hemianopia, but apart from that element was a poor player. When warned in a friendly way that an important piece was being attacked, he saw the danger and prepared to defend, but forgot this and made some other move. In other words, he thought slowly, and his retentive memory was impaired.

Change of Personality.—The patient's wife was questioned about any change in his personality. She thought he was more irritable than he should be, and more than he had been before the operation. The patient himself stated that his wife found constant fault with the son and that the two did not get along at all. This constant conflict irritated him, and he tried to get away from the house. (Our own observation was to the effect that the wife really was irritating, because of hyperthyroidism. She was somewhat overactive and tended to dominate the home. She was an almost constant talker and had a somewhat rasping voice. It is probable that the patient's criticism was correct. If this is so, there was no discoverable change in his personality.) He was deliberate and extremely thorough and persistent.

Comment.—In this case the picture also conformed to the general type of major temporal lobectomy. The patient spoke better than any of the patients in the other cases reported and was able to carry on conversation for a longer period than others. Yet the same inability to comprehend spoken language was present when speech came fast. He also had great difficulty with reading and writing.

CASE 3.—*Epileptic seizures for fifteen years. Three episodes of cerebral vascular accident; after the second great difficulty in comprehending spoken language. The patient spoke in short sentences, with paraphasia. Marked general defect of memory. Ability to read. Death after three years from thrombosis of the basilar artery. Autopsy: (1) old softening of the left lenticular nucleus; (2) destruction of the left angular gyrus and entire temporal lobe, except the tip; (3) recent softening of the right margin of the cerebellum, and (4) acute occlusion of the basilar artery without softening. The clinical picture represents the results of destruction of the left temporal lobe.*

Mrs. A. W., a white woman aged 57, was admitted in coma on July 14, 1937. She was irritable and responded to painful stimuli with a cry, but did not speak. The body temperature was 100.2 F., the pulse rate 92 and the respiratory rate 28 per minute. Her eyes did not fix, but roamed in all directions. The pupils reacted, though not quickly, to light. The vessels of the fundi were severely

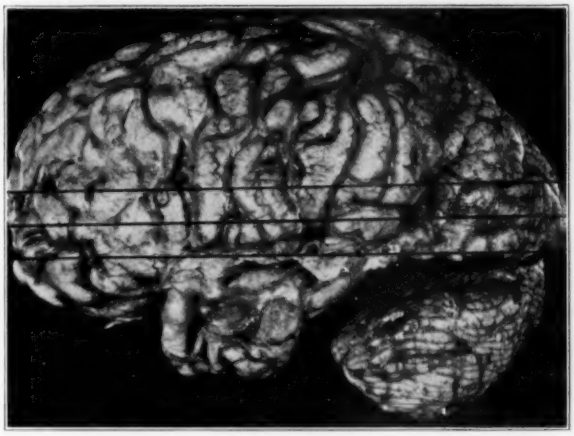

Fig. 2.—Lateral view of the brain in case 3. The lines indicate the planes of section shown in figures 3, 4 and 5.

sclerosed. The heart was essentially normal; the blood pressure was 220 systolic and 110 diastolic. There was a Babinski sign bilaterally. The extremities were spastic and resisted motion, the left upper limb less. The right arm was in hemiplegic contracture, and there was ankle clonus on the left. The deep reflexes were symmetric and increased; the abdominal reflexes were absent. Hoffmann's sign was present on the right. The patient died two days later, without having regained consciousness.

A history of the patient's earlier life was obtained from a son and a daughter, after autopsy had revealed the unusual condition described. Before marriage the patient had finished two years of high school and had then worked in department stores as a saleswoman. She had also done some artistic painting as an avocation, had made artificial flowers and had been "a great letter writer," i. e., she had been active in keeping up correspondence with friends. In all this diversified work she had always been right handed. In recent years she had been a Christian scientist and had therefore ignored illness. She lived during part of the time with

a sister of the same faith. (This must be taken into account in interpreting the statement that she had been in good health all her life until 1933, when she had illness which could not be ignored.)

She had been subject to epileptiform convulsions for fifteen years but her family considered her otherwise well until 1933. Change of eyeglasses was regularly attended to. In July 1933, during a period in which she lived alone, she was found one morning (by a sister who chanced to call) lying unconscious on the kitchen floor. She recovered half an hour after she was found and resumed her work the same day.

She was then considered well again until August 1934. On a certain Sunday she had spent the entire day attending church service; on arriving home that evening, at about 10 o'clock, she was unable to unlock the door with the key which

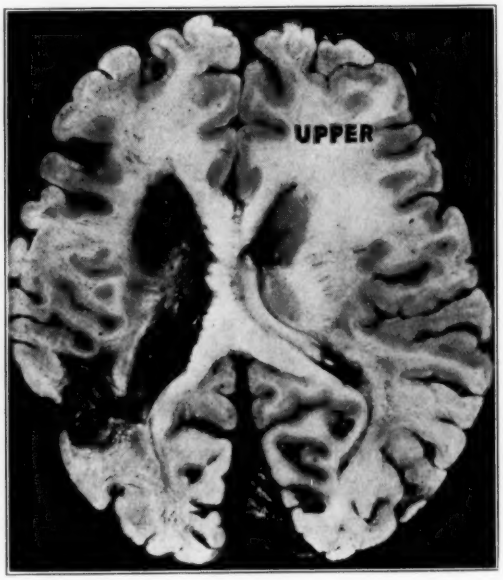

Fig. 3.—This section, the uppermost, shows the completeness of destruction of the angular gyrus, with a hemorrhagic cyst communicating with the lateral ventricle.

she carried. She called on the landlord, who lived in an apartment above, and obtained help. To the landlord she seemed very weak, and he was uneasy about her. On the following morning, when she did not appear after a few hours, his wife investigated and found the patient semiconscious, still in bed. She did not breathe stertorously "nor foam at the mouth, but was unable to talk or give an account of herself." She did not respond when spoken to and "did not seem to be entirely aware of her surroundings."

After this she was unable to take care of herself, and was therefore taken to live with her daughter. She gradually regained power to speak, but did not speak clearly unless she was excited or angry. At such times she suddenly spoke without any dysarthria. Furthermore, her sentences were always short, and she often used the wrong word to express herself. For example, she said: "Turn

out the fire," when she meant: "Turn out the light." However, after she had learned again to talk the daughter had no difficulty in comprehending what the patient meant.

Her comprehension of spoken language was more defective. She could not follow the trend of spoken language unless one spoke slowly and in short sentences. She attended church services regularly until her last illness, in 1937, but it was difficult to know how much she comprehended of the spoken language. She avoided becoming involved in conversation with friends at church because she felt inadequate to take part and confined her speech to such casual conversation as the time of day.

On the other hand, she was able to read. She read the newspapers and her lessons in a church manual, and took her church "quarterly" regularly and read it.

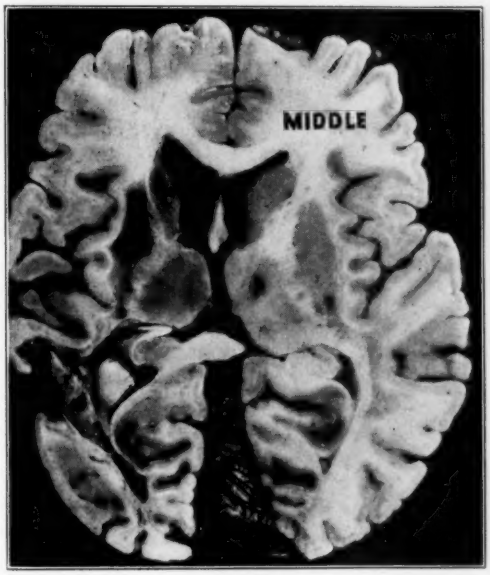

Fig. 4.—Destruction of the angular gyrus is evident also in this, the second section.

When fitted with glasses shortly before her last illness, she read every word of the small print. She also read novels, of which she kept half a dozen about the house. These she read and reread innumerable times. She never remembered anything she heard or read for more than a day, often not for more than an hour; she thus was entertained time and again by the same novels and considered them new each time. In the interpretation of this "reading" one might question how complete the process was. Certain it is that she gathered information from printed matter, so we shall consider that she read, but she did not retain the information except for a very brief period.

Her general memory defect was to the family the outstanding difficulty. She was not able after the episode of August 1934 to take care of the house, order food or plan meals. This was mostly because of the general loss of memory. When she went to the market she could not remember what to get if there were more than two things. She could not write because of paralysis of the right arm,

which never disappeared, although the leg recovered enough for her to walk to church and do work about the house. She therefore never wrote notes for herself, chiefly, she said, because she could not write well enough with the left hand. Concerning her ability to calculate it was difficult to obtain definite information. Her family could not depend on her calculating the change correctly, but always gave her small amounts; they depended on the merchant to give her the correct change. They thought she would not have been able to remember how much money she had had.

Concerning comprehension of music, it is known only that she listened to the radio and enjoyed the "music."

Her personality was distinctly changed after the episode of August 1934. She was more irritable, impatient and excitable. The family considered this to be

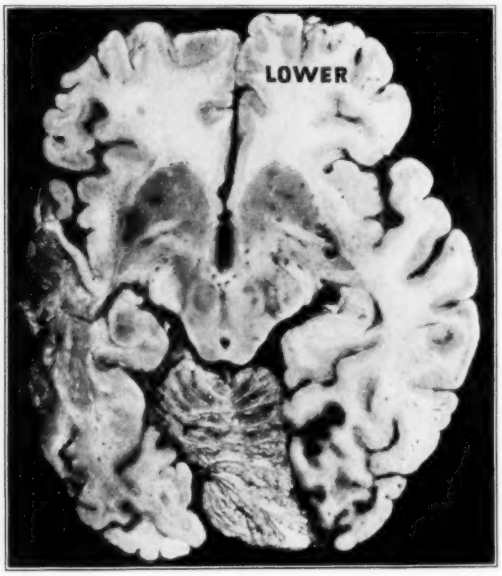

Fig. 5.—This section shows the destruction of the temporal lobe except for the extreme mesial portion.

due to her greater difficulty in comprehending and speaking. She always made mistakes and always gathered information incompletely and imperfectly, and therefore felt excluded from much of what went on about her. Evidence of visual defect which might be interpreted as hemianopia could not be obtained.

This was her condition up to a point just prior to her last illness. On the morning that she was taken to the hospital her daughter thought she did not look as well as formerly and advised her to remain in bed. When she went to work she said "good-bye" to the patient, who replied; "I'll be all right. I'll get up after a while." During the morning she was found unconscious; she did not regain consciousness.

Autopsy.—The left temporal lobe was practically nonexistent, except for the tip. The left angular gyrus was replaced by a hemorrhagic cyst, causing the left lateral ventricle to communicate with the surface. The ventricle was dilated (figs. 2, 3, 4 and 5).

The fact that the patient never learned to write with the left hand is ample proof, if any is needed, that she was right handed. As writing is the most complex function of language, it is not strange that this was the function which was not learned. It is remarkable that she learned as much as she did. Her comprehension of spoken language was almost identical with that of the patients who had had left temporal lobectomies, as already described. The most surprising fact was her ability to read with absence of the angular gyrus. Henschen has observed such cases, but they are rare. We must postulate that the right angular gyrus was able to take over the function of recognition of letters and words in this case. The pronounced general amnesia is somewhat strange, considering the location of the lesion.

CASE 4.—This case is not reported in detail because the manifestations of deprivation were relatively minimal. The patient was operated on by one of us (R.) for an astrocytoma of the right temporal lobe and the lobe removed. Prior to the surgical procedure the aphasic manifestations were slight. For four weeks the patient, who was a German-born sailor and able to speak, in addition to his native language, Danish, Norwegian, Swedish, Dutch and English, was unable to spell "Deutschland," "America," "California" or other simple words. He also was unable to calculate or to count correctly in Danish or Swedish, although he could still count in English, German and Dutch. It was clear that his concepts had suffered considerably, and we are compelled to assume that the right temporal lobe functioned to some extent in language before the operation. However, the left lobe took over all the function after about five weeks, as shown by the fact that all these defects had disappeared at the end of that time. This case is possibly exceptional; one must avoid generalizations on the basis of it.

GENERAL COMMENT

In view of these cases and with the thoroughly established fact that as a rule patients with vascular lesions of minor degree in the major temporal lobe make a poor recovery, the idea suggests itself that in selected cases in which recovery is bad and the general condition permits it may be justifiable to perform lobectomy. Removal of the damaged lobe, which seems to be a handicap to the remaining one, may give rise to considerable clinical improvement. This has not been tried because of the absence of proof of the proposition and the lack of a suitable case in which relatives strongly favored action. In such cases the patient himself, unfortunately, cannot be consulted, and much responsibility must rest on the surgeon. In cases of severe arteriosclerosis or of embolism resulting from such conditions as endocarditis or phlebitis, the underlying disease may completely contraindicate lobectomy. The results so far, however, are encouraging to the surgeon when called on to operate within the "language area" for a malignant neoplasm.

SUMMARY

Three new cases in which aphasia was studied after major (left) temporal lobectomy, performed surgically in 2 instances and by nature (thrombotic softening) in 1, and 1 case of minor (right) temporal lobectomy are reported. The similarity (almost identity) in the conditions of the patients in the first group in all cases so far studied places their remarkable capacity in language beyond coincidence and suggests that patients with complete loss of the major temporal lobe perform better than those with mere damage to it. Evidence is also presented that the minor temporal lobe may have considerable function in language even when the major lobe is intact.

ACTION POTENTIALS OF MUSCLES IN NORMAL SUBJECTS

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A study of the general physiology of the innervation of normal striated muscle in man may safely be limited to a few basic features. It is justifiable to assume that in most respects the muscles of the normal human being behave like those of other mammals, which have been the subject of numerous investigations. Some aspects of muscular activity, for example voluntary contraction, which differs in important respects from the results of electrical stimulation or of reflex innervation, are more readily observed in human subjects than in animals.

The neurologic disorders to which man is subject present an opportunity for the study of the physiology of striated muscle which is in many ways unique, as they can be duplicated only to a small extent by mutilating experiments on animals. In the course of various diseases muscles can be observed under the influence of a great variety of conditions, some of which throw considerable light on normal physiologic behavior. Later papers will be concerned with the phenomena observable under pathologic conditions, their interpretation and practical significance; the present article will be devoted to the physiologic responses of normal muscle.

The literature on muscle action potentials in man has grown large since the first reports of Piper [1] in 1907 and Buchanan [2] in 1908.[3]

This is the first of a series of clinical and experimental studies of motor disorders.

Part of the expenses of this investigation were defrayed by a grant from the Emerson Foundation.

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

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2. Buchanan, F.: The Electrical Response of Muscle to Voluntary, Reflex and Artificial Stimulation, Quart. J. Exper. Physiol. **1**:211, 1908.

3. J. F. Fulton (Muscular Contraction and the Reflex Control of Movement, Baltimore, Williams & Wilkins Company, 1926), K. Wacholder (Willkürliche Haltung und Bewegung insbesondere im Lichte elektrophysiologischer Untersuchungen, Ergebn. d. Physiol. **26**:568, 1928) and E. A. B. Pritchard (Electromyogram of Voluntary Movements in Man, Brain **53**:344, 1930) have reviewed the older literature extensively.

Progress in the investigation both of normal and of pathologic phenomena has been largely determined by refinements in the recording technic.

An especially important advance was the invention of the coaxial needle electrodes by Adrian and Bronk,[4] which made it possible, within certain limitations, to study the electrical changes produced by motor units, comparatively small bundles of muscle fibers innervated by the branches of the axon of one anterior horn cell. It has been generally accepted that sustained contraction of muscle is produced by repetitive nerve impulses. Sherrington and Eccles [5] had shown that action of muscle is managed by activation of a portion of the motor units available in a given muscle. Apparently, never are all active at the same time. Forbes [6] has suggested that motor units act in "rotation." There seem, however, to be no data on the mechanism of timing of different motor units. No unanimity of opinion exists in regard to their behavior with increasing effort, or even concerning the total number and shape of the electrical impulses recorded from a whole muscle. The chief problems in regard to the interpretation of the electromyograms obtainable from normal muscles appear to be reducible to four questions.

First, what is the form of the single impulse transmitted by the normal lower motor neuron to the muscle? Does it fit in with the conception of the physiologic behavior of striated muscle in lower animals? Can its refractory period be determined, directly or indirectly? Second, what are the upper and lower limits of the frequency of impulses recorded from the whole muscle and from its motor units during voluntary contraction? Third, how do the various motor units of one muscle act during voluntary contraction? Fourth, how does variation in strength of contraction involve form and frequency of the potentials recorded both from motor units and from the whole muscle?

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4. Adrian, E. D., and Bronk, D. W.: The Discharge of Impulses in Motor Nerve Fibres: II. The Frequency of Discharge in Reflex and Voluntary Contractions, J. Physiol. **67**:119, 1929.

5. (*a*) Sherrington, C. S.: Quantitative Management of Contraction in Lowest Level Co-ordination: Hughlings Jackson Lecture, Brain **54**:1, 1931. (*b*) Eccles, J. C., and Sherrington, C. S.: Numbers and Contraction Values of Individual Motor Units Examined in Some Muscles of the Limb, Proc. Roy. Soc., London, s.B **106**:*326*, 1930. (*c*) Cooper, S.; Denny-Brown, D. E., and Sherrington, C. S.: Reflex Fractionation of Muscle, ibid. **100**:448, 1926; Interaction Between Ipsilateral Spinal Reflexes Acting on the Flexor Muscles of the Hind-Limb, ibid. **101**:*262*, 1927.

6. Forbes, A.: The Interpretation of Spinal Reflexes in Terms of Present Knowledge of Nerve Conduction, Physiol. Rev. **2**:361, 1922.

These questions should receive an answer before any extensive interpretation of electromyograms obtained during disease states is undertaken.

TECHNIC

Observations were made on 12 normal adult subjects. In addition, a record from 1 patient and one from an experimental animal will be included.

Recording Systems.—Most of the records were taken with a cathode ray oscillograph. This apparatus, with a fairly low amplification and rather small coupling links between the different stages, was designed by L. Garceau as a clinical electromyograph. It is an extremely compact instrument and, within certain limitations, is very useful for the recording of spike potentials. In the oscillograph used in these experiments all the slower frequencies are completely suppressed, owing to the small capacity of the coupling condensers. The elimination of the slow frequencies has in itself a great number of apparent advantages. The spikes thus recorded stand out clearly, but their shape cannot be analyzed from the records. The sensitivity at optimal gain, which was invariably used, is 10 mm. per hundred microvolts on the 3 inch (7.6 cm.) screen. The deflections of the screen were photographed on 35 mm. film at the ratio of 3 : 1. The calibration on all the films therefore is 3.3 mm. per hundred microvolts. The speed of the camera at its best is 35 cm. per second; the timing is in flashes at one-sixtieth second intervals on all these records.

Another recording instrument at our disposal was a six channel, high amplification system, with which ink writers were used in the last stages. It had been designed by A. Grass for the purpose of electroencephalography. Owing to the use of large coupling condensers, it does not distort even very slow potential changes, while the ink writers follow frequencies up to 90 per second with complete fidelity. It is therefore a good supplement for the cathode ray oscillograph just described. Six records may be taken simultaneously. The gain is high. For the tracing of muscle potentials a sensitivity of 3 mm. per hundred microvolts is found sufficient, which makes the records easy to compare with those taken with the oscillograph. The records are written on paper 12.5 cm. in width, moving at a maximal speed of 6 cm. per second.

Two experiments to be reported here had been carried out by one of us [7] several years ago with a third setup, consisting of a condenser-coupled amplifier system with a Siemens oscillograph in the last stage. This is a mirror–turn coil type of galvanometer, with the coil reduced to a loop suspended in oil for damping. The inertia is very small, so that the system follows up to 3,500 periods per second with complete fidelity. The condensers were chosen large enough to allow undistorted reproduction of sinusoidal oscillations down to a frequency of 2 per second.[8] The gain in the experiments reported was varied from a deflection of 25 mm. for 10 millivolts to one of 60 mm. for 1 millivolt. The recording camera consisted of a drum covered with a sheet of bromide paper, 8 by 22 cm., rotating on the axle of a high speed motor, with a maximal peripheral speed of 6.8 meters

7. Hoefer, P.: Versuche über Nervenaktionsströme: II. Nerv-Muskel-Beziehungen, Ztschr. f. Biol. **93**:335, 1933.

8. Hoefer, P.: Versuche über Nervenaktionsströme: I. Technik und Methodik, Ztschr. f. Biol. **92**:228, 1932.

per second. With the shutter open the light beam writes a constant base line, and the potentials recorded will be seen as deflections superimposed on it. This mechanism allows close analysis of a spike, since one millisecond is represented by a distance of up to 6.8 mm. on the original record.

For a few control experiments a large Cambridge galvanometer was used. The optical magnification was 480, the calibration being so chosen that 1 millivolt caused a deflection of 10 mm. at a distance of 1 meter from the instrument.

Electrodes.—Potentials were recorded in these experiments from single muscles, from synergistic muscle groups and from motor units. For the tracing of potentials of whole muscles, surface electrodes of suitable sizes varying from 1 to 4 sq. cm. were usually used. The electrodes were applied to the skin with collodion (using a standard method of Dr. F. A. Gibbs); in other instances metal band electrodes were tied over the muscle, with electrode paste applied to the skin for better contact. In one experiment two needles were inserted into the biceps muscle for recording. For tracings from motor units coaxial electrode needles (gage 26 and 27) were used, in which the exposed area of the core is about 0.00024 sq. cm., while its diameter is 0.126 mm. The outside of the needle was grounded. Subjects and input leads were shielded in a grounded Faraday cage.

THE SINGLE MUSCLE ACTION POTENTIAL

The potential change during muscular contraction consists of a sequence of diphasic waves. This was observed by the earliest investigators [9] and has been accepted since. It is generally agreed that each of these diphasic waves is a single action potential. Piper's [10] records indicated that their frequency was constantly one of about 50 per second and that their pattern was approximately that of an alternating current (fig. 7), with smaller waves of a higher frequency *Nebenzacken* occasionally superimposed on the main waves. The constancy of Piper's 50 per second rhythm has been disputed by other investigators from the beginning.[11] However, little attention was paid to the actual time relations of the single spike and the obvious inconsistencies in Piper's original conception, which on the whole has been held valid by a number of later investigators, up to the present day.

In figure 1 a human muscle action potential is shown, traced by one of us in 1933 during a course of experiments on the refractory and irresponsive periods of motor nerve and striated muscle. The potential is that of a biceps muscle, stimulated from its motor point by induction break shocks applied by a small pad electrode. The stimulus used in this

9. Buchanan.[2] Piper.[1]

10. Piper, H.: Elektrophysiologie menschlicher Muskeln, Berlin, Julius Springer, 1912.

11. Garten, S.: Ueber die zeitliche Folge der Aktionsströme im menschlichen Muskel bei willkürlicher Innervation und bei Erregung der Nerven durch den konstanten Strom, Ztschr. f. Biol. **55**:29, 1910. Buchanan.[2]

instance had twice the strength of a threshold stimulus. Stronger stimuli could not be used, for obvious reasons. The action potential was recorded with two needle electrodes inserted in the muscle and traced with the Siemens oscillograph and the high speed camera. It appears as a spike with after-discharge. The height of the spike is reached in less than five-tenths millisecond. The voltage reached at the peak is a little over 15 millivolts. The duration of the spike part of the potential is about one millisecond. This does not express the true duration of the excitatory process, as would a monophasic lead. It shows, however, a marked difference from the diphasic elements in, for example, Piper's records obtained under comparable conditions, each one of which lasted about twenty milliseconds (fig. 7). The conclusion seems unavoidable, therefore, that a true "50 per second" rhythm or any action potential pattern of muscular origin should consist of widely separated, discrete spikes.

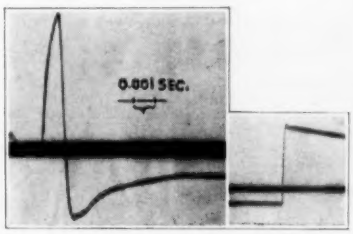

Fig. 1.—Action potential of the human biceps brachii muscle under direct stimulation (Hoefer [7]). Two needles were inserted in the muscle as recording electrodes. Note the shape of the spike and the duration of its rise. Time: The distance for one millisecond is marked. Calibration: Rectangular current, electromotive force of 10 millivolts. Siemens oscillograph.

At the same time [7] it was shown that in frogs, as well as in mammals, the refractory period of a motor nerve and the irresponsive phase of the striated muscle which it innervates are identical. No valid determination of a refractory period on a human subject was made, though it was attempted. Figures thus obtained, however, were in the same range as those found in experiments on mammals with adequate stimuli, and were in accord with those reported by Erlanger and Gasser [12] and by Forbes.[13] It seems to be a safe extrapolation, therefore, to assume that conditions

12. Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activity, Philadelphia, University of Pennsylvania Press, 1937.

13. Forbes, A.: The Mechanism of Reaction, in Murchison, C. A.: A Handbook of General Experimental Psychology, Worcester, Mass., Clark University Press, 1934, chap. 3.

are about the same in man, that the lower motor neuron has a refractory period of about five-tenth millisecond. Thus, it could carry up to 2,000 impulses per second.

The action potentials in response to direct stimulation over a nerve point are those of a whole muscle brought to synchronous discharge of all or of a greater part of its elements. It has not been possible to stimulate single motor units normally in the same way. In certain diseases, probably because of degeneration of peripheral neurons, fibrillary twitchings occur in diseased muscles, and it is possible at times to trace spikes of a single motor unit. The upper part of figure 2 is a record of a spontaneous discharge of a single motor unit obtained with a cathode ray oscillograph and coaxial needle electrodes. Between the well marked spikes discharges of a second motor unit are seen, small but distinctly visible, apparently farther away from the recording needle tip.

The normal proprioceptive reflex action potential, seen in the lower part of figure 2, in response to stimuli of increasing strength is similar

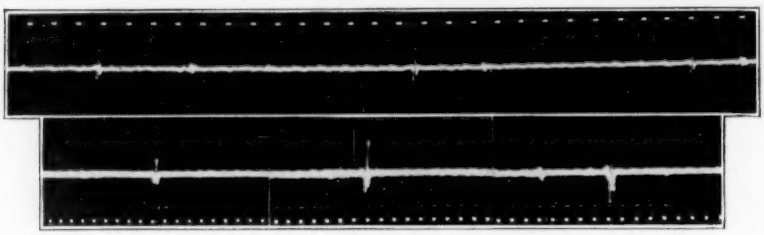

Fig. 2.—Upper tracing: rhythmic discharges of a single motor unit at the rate of 5 per second; coaxial needle electrodes. The subject suffered from amyotrophic lateral sclerosis.

Lower tracing: three normal ankle jerks in response to stimuli of increasing strength; surface electrodes.

Time for both records: one-sixtieth second intervals between flashes. Cathode ray oscillograph.

to the two other types of spikes described here. They were recorded with surface electrodes and show again what appears to be synchronized discharges of many motor units throughout the whole muscle, similar to the response produced by direct electrical stimulation.

ACTION POTENTIALS DURING VOLUNTARY CONTRACTION

Records were made from the biceps brachii muscle, from the flexor and extensor muscles of the forearm and from the rectus femoris muscle. Leads were taken from the whole muscle and from one to three of its motor units, simultaneously or successively under reasonably equal con-

ditions. The spikes were counted, usually for stretches of several seconds, during the different phases of the contraction, particularly during its height.

The study of moderate contraction is for several reasons a better approach to the understanding of the physiologic function of muscle than that of extreme and violent efforts. The potential changes during

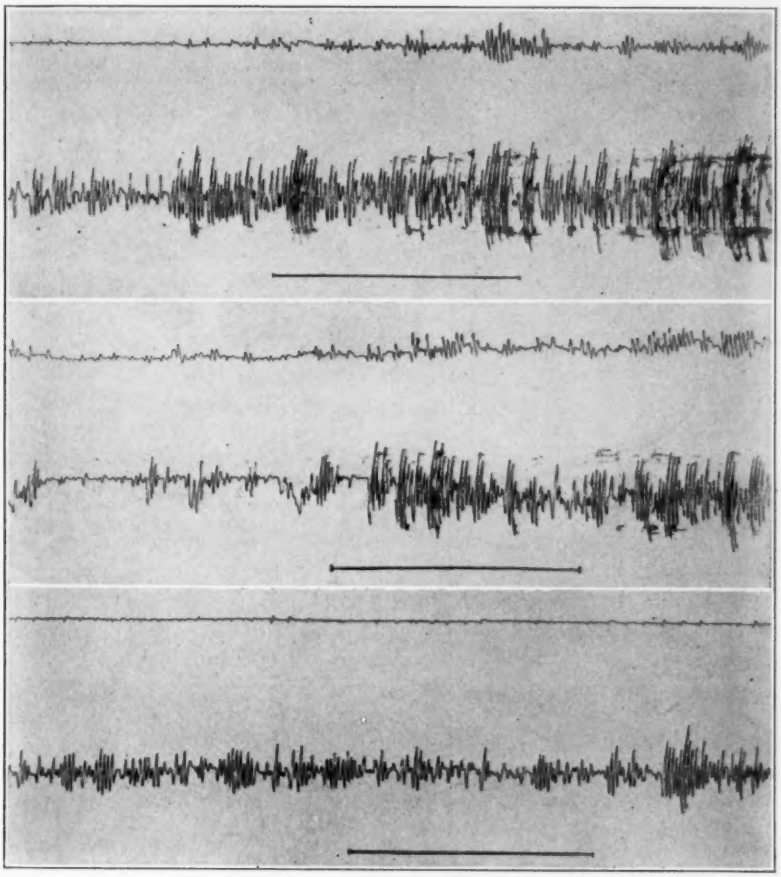

Fig. 3.—Three parts of a simultaneous record of two motor units of the rectus femoris muscle during mild contractions, taken with two pairs of coaxial electrodes. Note independence of the leads in frequency and pattern of spikes and the variations in size of the spikes. Time is marked as distance for one second. For details, see the text and table 1. Ink-writing oscillograph.

gentle contraction were, therefore, traced in the following two experiments, in which two and three pairs of coaxial needles were placed, respectively, in the rectus femoris muscle and simultaneous leads were recorded with the ink-writing amplifier. Figures 3 and 4 show parts

of the records, while in table 1 spike frequencies for both experiments will be found. In one of the experiments, a record of the activity of the whole muscle was made subsequently with surface electrodes placed over the same area and with the cathode ray oscillograph.

The records show complete independence of the motor unit leads. During a sustained effort they may start and stop discharging independently, and while the frequency in one of them increases it may

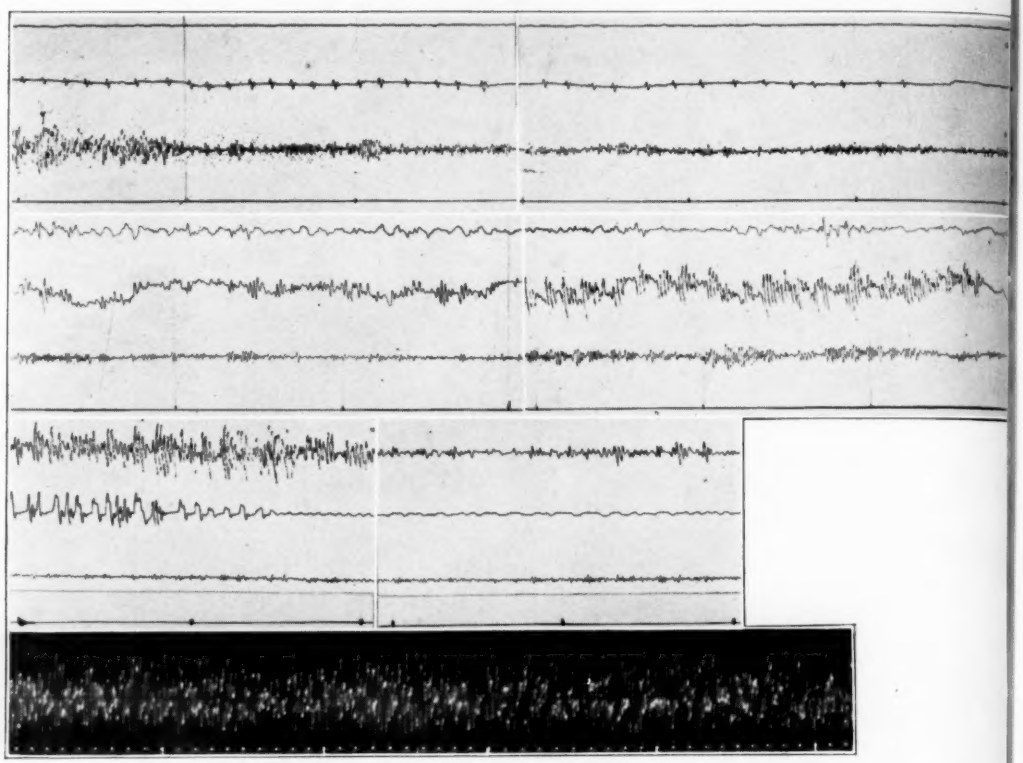

Fig. 4.—Simultaneous records of three motor units of the rectus femoris muscle during mild contraction, taken with three pairs of coaxial electrodes.

First row: The upper unit is inactive for six seconds; the middle unit shows 6 to 7 spikes per second, then stops suddenly; the lower unit is constantly active, but the intensity differs.

Second row: All three units are active; the upper unit shows a few artefacts between spikes; maximal activity has shifted to the middle unit.

Third row: Maximal activity has shifted to the upper unit; the middle unit shows a few artefacts between spikes, stops suddenly and stays inactive; the lower unit shows mild activity only. For details, see text and table 1. Time is shown in one second intervals. Ink-writing oscillograph.

Below: Record of mild contraction of whole muscle; surface electrodes. Time is expressed in one-sixtieth second intervals between flashes. Cathode ray oscillograph.

TABLE 1.—*Spikes Counted in Simultaneous Leads from Several Motor Units of the Rectus Femoris Muscle, from Records from Two Normal Men*

A. Records for T. P.*

	Proximal Unit, Frequencies per Sec.	Distal Unit, Frequencies per Sec.	Comment
1	33	56	1 sec. run
2	32 35 42 54	57 60.5 60 59	Four runs of 2 sec. each, contraction gently increasing in strength; increase limited to "proximal" unit
3	16	47	1 sec. run; beginning of contraction
4	15	43	1 sec. run, about 1.5 sec. later than part 3
5	13.5 15	52 50	2 runs of 2 sec. each, immediately following part 4. Contraction continued, but this time the proximal unit took no part, the distal unit very little
6	39	57	1 sec. run; slightly more vigorous contraction
7	8.5	38	Run of 2 sec. while the muscle is being relaxed
8	18.5 14.5	56 58.5	Two runs of 2 sec. each; muscle kept under slight constant contraction
9	0 0 0	29.5 24 24.5	Three runs of 2 sec. each; proximal unit has completely ceased discharging

* There are nine parts of the record, varying from one to eight seconds. Frequencies are given as per second, the figures for the two second runs being averaged for one second each (see fig. 3).

B. Records for P. H.†

	Proximal Unit, Frequency Lead 2	Intermediary Unit, Frequency Lead 3	Distal Unit, Frequency Lead 4	Comment
1	0 0 0 0 0 0	7 8 6 6 6 2‡	65 54 61 54 53 59	Six seconds in succession. Lead 2 inactive all the time; lead 3 shows a low frequency rather regularly until it fades out, while lead 4 is active (see fig. 4, upper part). Slight contraction
	Intermediary Unit, Frequency Lead 2	**Proximal Unit, Frequency Lead 3**	**Distal Unit, Frequency Lead 4**	
2	17 21 18	35 36 39	56 47 30	Three seconds in succession. Large waves and garlands in leads 2 and 3 are artefacts produced by motion (see fig. 4, 2d row, 1st record)
3	19 18 21	40 45 32	60 59 47	Three seconds in succession; relaxation toward end (see fig. 4, 2d row, 2d record)
4	45 44	29 13	27 35	Two seconds in succession (see fig. 4, 3d row, 1st record)
5	31 36	0 0	39 41	Two seconds in succession, following part 4 closely (see fig. 4, 3d row, 2d record)
6	Whole muscle surface lead (see fig. 4, bottom), counted for 2 sec. in succession			
		328 276		

† Channels for the two first leads were exchanged during this experiment. The whole muscle lead with surface electrodes over the same area was recorded subsequently, with the cathode ray oscillograph (see fig. 4). Six runs of two to six seconds' duration were counted here.

‡ Dropping out.

decrease in another. There is a definite trend toward increase in rate when the strength of contraction is increased, though even then, but especially as effort is decreased, one unit may drop out completely. The frequencies vary between 6 and 60 per second. The patterns in the different leads vary in regard to grouping and amplitude as much as the frequencies do, but the single spikes are obviously equal in duration. The cathode ray record shows frequencies of about 300 per second. During complete relaxation no activity is seen.

The spike pattern is somewhat different for stronger effort. In a group of experiments coaxial electrodes were placed in the biceps brachii muscle, and the subject was asked to pull rather strongly against resistance. This was repeated immediately afterward with about equal effort, but with surface electrodes placed over the muscle. In figure 5 responses recorded with the coaxial electrodes (above) and those from the whole muscle (below) are shown. The spike frequencies for both

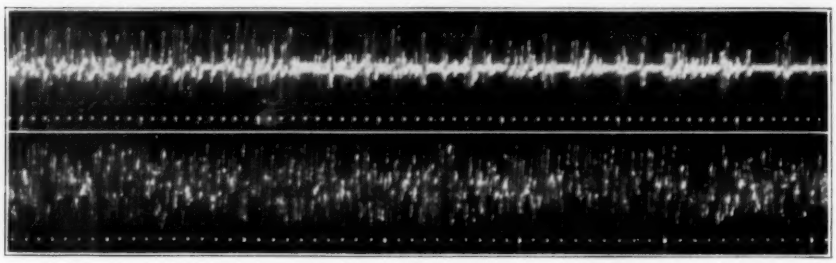

Fig. 5.—Records during medium strong contraction of the biceps brachii muscle. Above, response for a motor unit; below, response for whole muscle. Time is expressed in one-sixtieth second intervals between flashes. Cathode ray oscillograph.

leads in this and in a similar experiment are given in table 2. It is easily seen that the spikes are both much less frequent and less regular in the record from the motor unit lead, the last part of which shows the beginning of relaxation. The size of the spikes varies in both leads. Some "background" activity is seen in the motor unit lead, but the spikes are clearly distinguished. It is difficult at times to separate the spikes in the whole muscle lead. It is justifiable, therefore, to assume that the actual number of spikes is somewhat higher than the number counted with this lead and with our recording speed.

While in gentle effort the relation of the spike frequencies of motor unit and entire muscle varies between 1 : 50 and 1 : 5, the relation for stronger (not actually maximal) effort is roughly 1 : 3.

During extreme effort the spike frequencies in both leads may become much closer. Data from a striking instance are presented in table 3. This experiment was one of a series in which the electrical activity for both leads was compared in graded efforts up to the extreme. Among

other devices, a clinical dynamometer was used. This consists of a strong elliptic steel ring to be compressed in the direction of its lesser diameter. It is calibrated in pounds. The subject was asked to hold the dynamometer in his left hand and to exert a sustained pressure of 25 pounds (11.3 Kg.), then of 50 pounds (22.7 Kg.), and finally to use all his strength. The maximum for a right-handed subject was about 75 to 80 pounds (34 to 36.3 Kg.).

The figures thus obtained for the motor unit leads are still consistently below those for the whole muscle. The ratio here is one of

TABLE 2.—*Spike Frequencies Per Second for Several Seconds in Succession in Motor Unit and Whole Muscle Leads During Contraction of Biceps Brachii Muscle in Two Normal Young Men*

A. Ra (see fig. 5)			B. Co		
Second	Motor Unit	Whole Muscle	Second	Motor Unit	Whole Muscle
1	113	320	1	135	225 (starting)
2	135	317	2	127	283
3	113	333	3	102	281
4	...	302	4	127	280
5	...	351	5	120	258
			6	126	199 (relaxing)
			7	65 (relaxing)	

TABLE 3.—*Spike Frequencies Per Second in Motor Unit and Whole Muscle Leads During Graded Contractions of Strong and Maximal Character in a Normal Right-Handed Man During Sustained Compression of Dynamometer with the Left Hand*

Dynamometer Readings	Motor Unit	Whole Muscle
25	187	235
50	275	320
75-80	350	437

4:5. It is conceivable that ultimately a ratio of 1:1 might be approached. The meaning of the two last groups of experiments depends largely on the reliability of the coaxial needle technic. We shall deal with this question later.

In these experiments two more features were noted. The amplitude of the spikes, as well as the frequency, increases with increasing effort. Furthermore, a tremor pattern visible both mechanically and in the grouping of the potentials may appear in extreme effort.

COMMENT

Certain properties of the single diphasic muscle potential in man have been studied. Evidence has been given to show that in man, as well as in other mammals, the absolute refractory period of motor nerve and striated muscle, that is, of the lower motor neuron, is about five-

tenths millisecond. Therefore it was postulated that the lower motor neuron should be able to carry up to 2,000 impulses a second.

Field and Brücke [14] stated that the refractory period of the frog's motor nerve is greatly increased by fatigue produced with continuous faradic stimulation. Using a different technic of stimulation and recording the potential responses with a variable gain, one of us [7] could not confirm this. It was seen in these experiments that the refractory period of a frog's sciatic nerve and that of its gastrocnemius muscle were identical before and immediately after prolonged indirect stimulation with far supramaximal stimuli. Under these conditions the threshold for the muscle rises to about twice its original value, while the amplitude of the muscle potentials falls to about one fortieth of its original size, or even less. The latter are rediscovered only with greatly

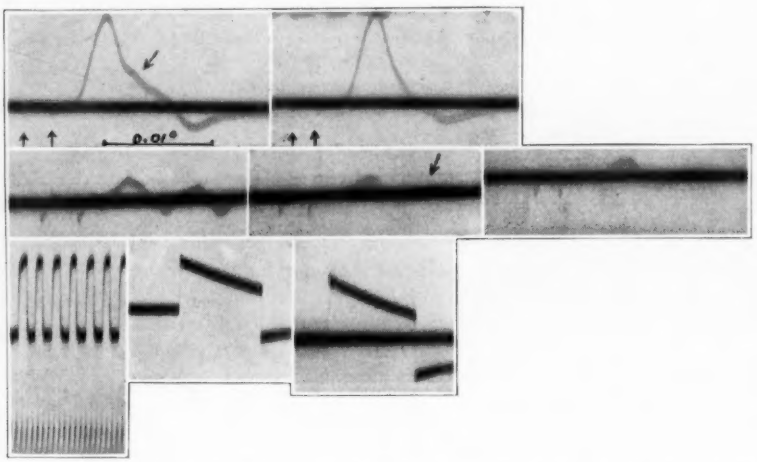

Fig. 6.—Absolute refractory period of frog muscle before and after fatigue. The first two records show action potentials, immediately before and at the refractory period, before fatigue. The following records show potentials much reduced in size by fatigue, again shortly before and at the refractory period. Fatigue was produced by application of 9,000 stimuli during five minutes. The form of the fatiguing current is shown. Calibration: 10 millivolts for fresh muscle; 3 millivolts for fatigued muscle. The second determination was made immediately after the end of the fatigue period. The temperature before was 15.5 C., and after, 14.4 C. The refractory period each time was two and five-hundredths milliseconds. Note stimuli artefacts. Time: Distance for one-hundredth second is marked on the first record. Siemens oscillograph.

increased gain. The determinations were made with a Helmholtz pendulum. The result appears to show that conduction of impulses in at least a portion of the structures involved withstands fatigue.

14. Field, H., and Brücke, E. T.: Ueber die Dauer des Refraktärstadiums des Nerven bei Ermüdung und Erholung, Arch. f. d. ges. Physiol. **214**:103, 1926.

The objection might be raised that recovery starts shortly after the prolonged stimulation is finished. The changes, however, which were still found and the fact that full recovery to the initial size of the potentials did not occur until twenty to thirty minutes later seem to prove that the muscles were actually still fatigued when the second determination was made. Figure 6 shows a record of one of these experiments.

The rigid conditions of an experiment for the determination of the refractory period do not exist in physiologic innervation. A unit, if active at all, is always maximally active. Still, even in maximal innervation [5b] only a majority, but never all, of the units are active. It may therefore be assumed that the possible number of impulses reaching a muscle might be even higher than the apparent limit given by the refractory period of the lower motor neuron.

It is obvious that a direct inference must not be drawn from these experiments as to the probable behavior of any central nervous structure. Thus, it has been shown by a number of investigators [15] that a frequency

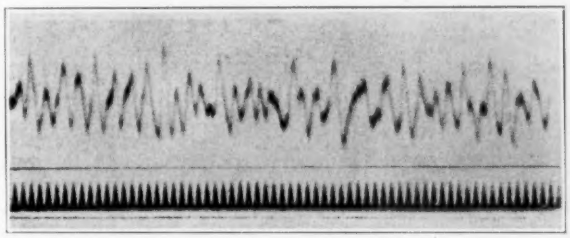

Fig. 7.—"Fifty per second" rhythm during voluntary contraction of human muscle, recorded with a string galvanometer. Time is expressed in one-hundredth second intervals (from Forbes [13]).

of 250 to 300 stimuli per second is about all a muscle will follow in reflex stimulation. This particular limitation, however, is not of necessity valid for central processes of other than reflex nature.

Piper's classic experiments have been discussed at great length in the literature and are too well known to need detailed description here. His string galvanometer records show invariably a rhythm of about 50 per second. He stated, furthermore, that a change in intensity of the contraction results only in a change of amplitude, not one of frequency, and that each diphasic wave is equivalent to a single action potential. According to his view, the rhythm of the muscle potentials is determined by central impulses running almost, but not entirely, synchronously to the single muscle fibers in salvos. This lack of complete synchronization

15. Cooper, S., and Adrian, E. D.: The Electric Response in Reflex Contractions of Spinal and Decerebrate Preparations, Proc. Roy. Soc., London, s.B **96:** 243, 1924.

results in superimposed secondary waves which may vary a great deal, but will never abolish the main rhythm of 50 per second.[16] A typical record taken from Forbes's monograph [13] is shown in figure 7. It has been possible for us to reproduce similar records with a string galvanometer. Adrian,[17] who pointed out the similarity of motor unit discharges and sensory messages, has shown that the string galvanometer is, for a number of reasons, technically unsatisfactory for the recording of short impulses of low voltage.

Frequencies of action potentials recorded from whole muscles in these experiments are entirely different from those of Piper. They range from slightly below 200 to about 450 a second and show a variation with the intensity of effort and, possibly, with the size of the muscle. (Mild contraction of the rectus femoris muscle produces between 276 and 328 spikes, while the flexor muscles of the forearm show a similar range for rather strong effort.) The increase of the amplitude with the effort, seen by Piper, could be confirmed. It seems reasonable to suppose that Piper's small secondary waves correspond to the discrete spikes recorded with the cathode ray oscillograph. The 50 per second rhythm found so constantly even in Piper's dynamometer experiment is hard to understand unless accessory hypotheses are taken into consideration, which will be dealt with later. The possibility of a compound of mechanical artefacts, partly muscular, partly due to the electrodes and to properties of the string, has to be considered.

It has been assumed by several authors [11] that no matter what the number of impulses reaching it the muscle will respond with an "intrinsic" rhythm of its own. Piper himself has disproved this assumption. Von Weizsäcker,[18] who in 1921 briefly reviewed the early literature since Piper, criticized the 50 a second rhythm and pointed out that "usually many more than 50 oscillations can be counted and that there is no rhythm as a rule." He found slow high waves in patients suffering from diseases of the posterior column and concluded that the proper motor rhythm is slow and that the normally high frequency is produced by proprioceptive impulses, by which the basic rhythm is split. Dusser de Barenne and Brevée [19] saw frequencies of 100 to 200 per second occur spontaneously in muscles during decerebrate rigidity. Section of posterior roots and cocainization of the posterior horns reduced the frequency to from 50 to 70 per second. This they said was the true muscle rhythm.

16. Piper,[10] pp. 101 and 102.

17. Adrian, E. D.: Die Untersuchung der Sinnesorgane, Ergebn. d. Physiol. **26**:501, 1928.

18. von Weizsäcker, V.: Ueber Willkürbewegungen und Reflexe bei Erkrankungen des Zentralnervensystems, Deutsche Ztschr. f. Nervenh. **70**:115, 1921.

19. Dusser de Barenne, J. G., and Brevée, J. F. G.: The Interpretation of the Electromyogram of Striated Muscle During Contractions Set Up by Central Nervous Excitation, J. Physiol. **61**:81, 1926.

Both observations, highly interesting as they are, can be explained in a number of ways and not necessarily have a bearing on Piper's observation on normal voluntary contractions. Furthermore, Cooper and Adrian [15] found, in spinal and decerebrate animals, that with strong electrical reflex stimulation of low frequencies secondary waves of higher frequency appeared between the primary waves. The secondary waves persisted even after the proprioceptor impulses were cut off by procaine hydrochloride. Cooper and Adrian suggested that secondary waves are the result of repetitive discharges. They expressed acceptance of Forbes's [6] theory of the repeated discharge of a motor neuron to a single afferent excitation.

Motor unit frequencies for mild effort ranged from 6 to 60 per second in our experiments. This is in accord with the figures reported by Adrian and Bronk [4] and by Lindsley.[20] Figures reported by Denny-Brown [21] and by Smith [22] were consistently lower and ranged in both instances between 5 and 20 a second. Denny-Brown, using a recording technic for motor units different from that of other investigators and employing minimal stimuli, did not see an increase in the frequency of an individual motor unit. In his experience, the increase in impulses with increasing stimuli was exclusively due to "recruitment" of new units in the sense in which this term was used by Liddell and Sherrington.[23] Smith employed frequencies below about 20 a second because with efforts causing a higher frequency she could see a "step-like onset of different units."

In our own records we see that increase and decrease of frequencies in individual units correspond in general to increase and decrease of contraction. This was observed by all investigators except Denny-Brown. It is not, however, an invariable rule because, as the records of simultaneous leads with increasing effort show, one motor unit may keep a constant frequency or even decrease in frequency and drop out, while another shows an increase. Correspondingly, during sustained effort frequencies are not constant but either vary in some of the units or decrease and increase in others independently. Lindsley [20] found a variation of rhythm of between 10 and 30 per cent during maintained effort, as we were able to confirm, though at times our variations were much higher (table 1). At times certain leads were not active at all, and at

20. Lindsley, D. B.: Electrical Activity of Human Motor Units During Voluntary Contraction, Am. J. Physiol. **114**:90, 1935.

21. Denny-Brown, D. E.: On the Nature of Postural Reflexes, Proc. Roy. Soc., London, s.B **104**:252, 1929.

22. Smith, O. C.: Action Potentials from Single Motor Units in Voluntary Contraction, Am. J. Physiol. **108**:629, 1934.

23. Liddell, E. G. T., and Sherrington, C. S.: Stimulus Rhythm in Reflex Tetanic Contraction, Proc. Roy. Soc., London, s.B **95**:142, 1923.

other times they started to discharge without any perceptible change in the condition of the experiment. The activity of the individual motor unit appears, therefore, to be irregular during mild effort.

The amplitude of the spikes from individual coaxial leads was at times constant; at other times there was a regular slow increase or decrease, which was apparently not steplike or quantal but steady, causing a smooth "staircase" transition. Both types of action can be seen at different times in one and the same lead, as figures 3 and 4 show.

Differences in discharge voltage of motor units in different leads could be explained in several ways. Their distances from the respective recording electrodes might be different. Or, as Eccles and Sherrington [5b] have shown, the units might differ in size and thus have different discharge voltages as well as contraction values. But differences in one and the same lead cannot be understood as easily and are at first sight hardly reconcilable with the "all or none" law. One lead might record the discharges of one or several units at the same time, according to variations of activity in its neighborhood. Different patterns might thus be produced. Still, it is hard to understand a pattern as regular as the "staircase" brought about in this way, and interference as well as superposition should be expected.

A better explanation might be that contraction and subsequent relaxation of a fiber group could change its spatial relation to the recording needle tip sufficiently to explain increase and decrease of the recorded potentials. A single group only slightly active and surrounded by a number of inactive groups, on the other hand, might stay fixed in its distance from the electrode, and that would explain the trains of identical spikes, usually seen at low frequencies.

Less probable is a third possibility, namely, that though the unit responds maximally, its different fibers are not all active at the same time. Lindsley [20] observed progressive diminution of spike amplitudes during fatigue, which might have a similar explanation. He did not report corresponding increases of amplitude.

No final explanation should be attempted, however, until parallel leads with several cathode ray tubes and with a high speed recording camera allow one to analyze properly the rate and form of discharge of individual units. It should be emphasized, however, that in a normal striated muscle during mild contraction activity is shifted from one place to another, without obvious regularity and not even always in accordance with the changes in the whole muscle. Forbes's [6] conception of "rotation" of motor units has not been held valid by the investigators [24] studying the motor unit in voluntary contraction. No evidence of "rotation" was found in these experiments. It is too early at this stage to

24. Adrian and Bronk.[4] Lindsley.[20] Smith.[22]

form a new conception of the way in which voluntary contraction is sustained. It is conceivable, however, that some alternating or shifting takes place by which fatigue is avoided.

While in mild contraction the frequencies recorded from different units simultaneously vary at a ratio of 1 : 10 and the frequencies of the individual unit still vary widely, values are far more uniform for strong or sustained efforts in successive leads and in different subjects performing similar tasks, as seen in table 2. Here the increase and decrease of frequencies and amplitudes with innervation and relaxation are clear. For extreme effort, as shown in table 3, the general features are similar, with correspondingly higher figures. In the interpretation of records obtained during more than mild effort, however, technical problems have to be considered. Adrian and Bronk [4] pointed out that "at present the method can only be used with certainty during weak contractions, where active fibre groups are some distance apart." The coaxial electrodes can record motor units at a distance, as shown in the upper part of figure 2, in which a distant motor unit is represented by small, but unmistakable, discharges in the background between the larger ones. Several units at about equal distance might be represented by spikes of about equal size, and a similar effect could be expected for units of a higher discharge voltage at a greater distance. In each group of experiments mere inspection of the records or counting of the spikes does not enable one to make a decision as to their origin.

In the observation of normal voluntary muscle action potentials we find no direct indication of the efferent central impulses, by which muscle activity is managed and regulated. We are able to conclude from the findings of Cooper and Adrian [15] that efferent central impulses alone and without participation of lower reflexes produce the ordinary pattern of voluntary contraction and we see increase in frequency of the motor unit discharges take place, but we do not know how these impulses are transmitted.

SUMMARY

Certain features of the normal action potential of muscle in man have been studied and discussed.

1. The single diphasic potential wave is of short duration, in the range of one millisecond. It has a spike character.

2. The absolute refractory period of the muscle potential is in the range of five-tenths millisecond.

3. There is reason to conclude, therefore, that the lower motor neuron in man is able to carry up to about 2,000 impulses per second.

4. Spike frequencies have been counted in motor unit leads and in whole muscle leads. Frequency and amplitude increase with increasing effort in both.

5. The frequency of discharge of the motor unit is found to be lower than that of the whole muscle. For gentle contraction motor unit frequencies were found to range between 6 and 60 per second, while the entire muscle discharges were about 300 spikes per second.

6. In gentle contraction, individual motor units are independent in their frequencies of each other and, to a certain degree, even of the nature and state of the contraction. Thus, the individual units may alternate in their activity, while muscular contraction is sustained without fatigue.

7. For medium strong and for strong effort no safe conclusion as to the motor unit frequency can as yet be drawn.

PERSISTENCE OF FIBRILLATION IN DENERVATED SKELETAL MUSCLE AND ITS NONOCCURRENCE IN MUSCLE AFTER TENOTOMY

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The object in this report is to record the persistence of fibrillation in denervated skeletal muscle, the occurrence of such fibrillation being already thoroughly documented (Schiff,[1] Langley and Kato,[2] Denny-Brown and Pennybacker[3]). Significance attaches to the duration of this activity because of the argument, originally presented by Langley[4] and recently reviewed by me,[5] that denervated skeletal muscle atrophies because it is fatigued by the ceaseless fibrillation. This interpretation contradicts the commonly held clinical view that denervation atrophy is the result of disuse. If the mechanism of atrophy is one of exhaustion by fibrillation, then the fibrillation must continue for a time commensurate with the time course of atrophy. That it does so continue will be demonstrated.

Because the atrophy of skeletal muscle which follows tenotomy and that which follows neurotomy have so frequently been considered as similar phenomena, and because Bosmin[6] has reported that tenotomized muscle also fibrillates, fibrillation was sought in tenotomized muscle, even though consideration (Tower[5]) of the probable mechanism of fibrillation scarcely permits of its occurrence in such circumstances. This examination was made largely in the same animals and under the

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This work was assisted by a grant from the Rockefeller Foundation.

1. Schiff, M.: Ueber motorische Lähmung der Zunge, Arch. f. physiol. Heilk. **10**:579 and 665, 1851.

2. Langley, J. N., and Kato, T.: The Physiological Action of Physostigmine and Its Action on Denervated Skeletal Muscle, J. Physiol. **49**:410, 1915.

3. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

4. Langley, J. N.: Observations on Denervated Muscle, J. Physiol. **50**:335, 1916.

5. Tower, S. S.: The Reaction of Muscle to Denervation, Physiol. Rev. **19**: 1, 1939.

6. Bosmin, O.: Sulla fibrillazione che accompagna l'atrofia del muscolo in vario modo immobilizzato e tentativi per prevenirla, Arch. d. sc. biol. **7**:341, 1925.

same conditions as those in which denervation fibrillation was under observation.

PROCEDURE AND RESULTS

The experiments were performed on 6 cats. In 5 of these, under ether anesthesia, the right brachial plexus and derivative nerves for the forearm were excised from high in the axilla to the elbow. Beginning forty-eight hours after the operation and repeating at two day, three day, weekly or monthly intervals, parts of the denervated muscle mass were exposed and examined for fibrillation, with the use of strong, oblique illumination and, when any uncertainty existed, a hand lens. Except at the terminal, and most extensive examination, aseptic technic was employed. All the superficial muscles of the forearm and the lumbricales and volar interosseous muscles of the paw were examined in this way, usually repeatedly. The examination for fibrillation was made sometimes with the animal under anesthesia induced by ether or pentobarbital sodium; more frequently, in view of the complete anesthesia of the parts, no anesthetic was used. The fibrillation is quite unaffected by surgical anesthesia with ether, chloroform or pentobarbital sodium, and even persists after the heart has stopped for from one to fourteen minutes, weakening progressively. Fibrillation was first observed on the seventh day after nerve section, but different muscles commence to fibrillate at such different times that not before the fourteenth day were all the muscles examined invariably found to be in fibrillation. Thereafter the phenomenon was always demonstrable in any muscle exposed.

The observations of Langley and Kato [2] on denervation fibrillation were verified in detail, 3 of the cats being killed during the first month after nerve section in this endeavor. On the disputed point of the unit in action in fibrillation—whether it is the single muscle fiber (Brown,[7] Denny-Brown and Pennybacker [3]) or a part only of one fiber (Langley and Kato [2])—my observation confirmed that of Langley and Kato. The length of fiber involved varied greatly, from a fraction of a millimeter to several millimeters, even in closely adjacent regions, but the length of the fibers under examination ranges from several millimeters, in the interosseous muscles, to as many centimeters, in some of the long muscles of the forearm. At any one spot the fibrillation retained its appearance of being coarse or fine throughout any given period of examination, even for several hours, unless conditions were materially changed, as by shutting off the blood supply or pushing anesthesia to the point of death. In the obscure matter of the effect of intravenous use of physostigmine my experience again repeated that of Langley and Kato. Physostigmine (0.2 to 0.3 mg. per kilogram with or without 0.1 mg. per kilogram of atropine sulfate) might have produced some slight augmentation of the fibrillation, but certainly this was not striking.

To the description by Langley and Kato several minor points may be added: The fibrillation was very susceptible to rough handling, to

7. Brown, G. L.: The Action of Acetylcholine on Denervated Mammalian and Frog's muscle, J. Physiol. **89**:438, 1937.

interference with blood supply and to cooling. Occluding the blood supply to the part by a constricting cuff well above the region, such as to the upper part of the arm when the volar interosseous muscles were under examination, abolished the fibrillation in one to two minutes, but on releasing the circulation the fibrillation rapidly reappeared. Cooling the muscle by applying a metal surface chilled to 10 C. also abolished the fibrillation. Warming the muscle by laying on a metal surface heated to 45 or 50 C. increased the vigor, and perhaps the rate, of the fibrillation and restored fibrillation when it had been suppressed by cooling and for a brief length of time after it had ceased in the dying animal. Warming did not, however, produce, fibrillation in muscle which had not yet begun to fibrillate after denervation, not even when it had already commenced in other parts of the denervated muscle mass.

The persistence of fibrillation in denervated muscle was established by repeated examination—in one cat over a period of six months and in another over one year. Regeneration of nerves and reinnervation of muscles were prevented in these 2 animals by reexposing and excising the stumps of the brachial plexus, once in the course of six months and twice in the course of the year's survival. At first some part of the denervated muscle mass was exposed each week, but after the second month the interval between examinations was lengthened to a month or more. By alternating between the volar and the dorsal surfaces of the forearms, with occasional exposure of the fifth interosseous muscle, no difficulty was encountered with infection and not much with scar tissue. The healing of these repeated incisions in an area of total denervation was speedy and uneventful. Atrophy progressed rapidly from the second week, and in the third month elbow, wrist and digits became set in flexor contracture. Fibrillation continued throughout the period of examination, even to a year, in all tissue recognizable as muscle, maintaining its original rate of the order of magnitude of 2 to 8 per second but becoming feeble in proportion to the wasting and paling of the muscle. In parts no longer recognizable as muscle by a peculiar translucency fibrillation was not visible. The interosseous muscles atrophied most slowly, preserving considerable bulk and red coloration to the ninth month, and these muscles fibrillated vigorously even after a year. In examining for fibrillation in these later stages care must be taken to bring the muscle tissue under direct observation without interposition of fascia or scar tissue, and even at the start fibrillation is not visible through a dense fascia, such as the antebrachial. Likewise, care must be taken that the muscles are not under tension, a condition not always easy to establish when contracture is strong. As Langley and Kato noted, putting the muscle under tension suppresses fibrillation completely, though whether this suppression is real or only apparent electrical records alone can tell, and this examination has not been made.

Tenotomized muscle was first examined for fibrillation in the 2 long-surviving cats. In the second month after section of the brachial plexus, one achilles tendon was cut in each cat and the gastrocnemius-soleus group of muscles subsequently exposed twice in each animal, one and four or two and four weeks after tenotomy. Pentobarbital sodium anesthesia was used for this and the occurrence of fibrillation in the denervated muscles of the forearm established either immediately before or immediately after examination of the tenotomized muscle. In another cat tendons were cut in both the foreleg and the hindleg (triceps, abductor digiti quinti and achilles), and thorough examination for fibrillation was made two weeks later, with the animal under ether anesthesia. In no case was fibrillation observed in any tenotomized muscle at any time after the tenotomy. With light anesthesia fine fascicular contractions were common during manipulation of the muscle or accompanying the generalized tremor of light anesthesia, but these, together with all gross forms of reflex activity, differ unmistakably from the phenomenon of fibrillation.

COMMENT

The spontaneous fibrillation which develops, after a lapse of days, when skeletal muscle is denervated continues unabated in rate and unaltered in properties but diminishing in strength for as long as the denervated muscle is recognizable as mucle, even to a year. The persistence of fibrillation is therefore such as to permit it to underlie the atrophy of denervated muscle. Tenotomized muscle, on the other hand, exhibits no trace of fibrillation, and hence some other mechanism must be sought for the atrophy which develops in this condition. Because the atrophy of tenotomy resembles the atrophy of neurotomy in gross morphologic aspects, and in chemical aspects so far as these have been examined (Grund,[8] Audova,[9] and Sato and Kasugai,[10] Hines and Knowlton [11]), except that it is slower to develop and less grave, an explanation for this lesser atrophy would be most acceptable if it corresponded in some way with the explanation offered (Tower [5]) for

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9. Audova, A.: Ueber den zeitlichen Verlauf der Muskelatrophie nach Sehnendurchschneidung, Schweiz. Arch. f. Neurol. u. Psychiat. **10**:211, 1922; Vergleichende Untersuchungen über die chemischen Veränderungen bei der Muskelatrophie, Skandinav. Arch. f. Physiol. **44**:1, 1923.

10. Sato, T., and Kasugai, F.: Ueber den Kohlehydrat und Energieumsatz im atrophischen Muskel, Tohoku J. Exper. Med. **26**:336, 1935.

11. Hines, H. M., and Knowlton, G. C.: Electrolyte and Water Changes in Muscle During Atrophy, Am. J. Physiol. **120**:719, 1937.

denervation atrophy. Rehn [12] expressed the opinion that the continuous small action potentials which he led off from tenotomized human muscle, beginning not, as with denervation, a few days but rather a few hours after operation, represented a *"tetanische Dauerreflex,"* while Davenport and Ranson [13] described tenotomized muscle as in contracture. Fairly clearly, tenotomized muscle is involved in a spasm of some sort, probably initially reflex but later set in myostatic contracture. Quite possibly this spasm may so exhaust the muscle that, like denervated muscle in fibrillation, it atrophies. If this is true, then the atrophy of denervation and the atrophy of tenotomy, together, perhaps, with the muscular atrophy of acute arthritis, which has been shown (Harding [14]) to involve an increased use of oxygen, and that of spastic upper motor neuron lesion, represent not atrophies of disuse but, on the contrary, the result of exhaustion of the muscle by excessive activities, in themselves of diverse mechanisms but operating to the similar end of atrophy of the skeletal muscle affected. The occupational atrophies described by Lorenz [15] represent a further, simpler example of atrophy of skeletal muscle in conjunction with overuse.

SUMMARY

The spontaneous fibrillary activity of denervated warm-blooded skeletal muscle has been shown to continue over a period commensurate with the continuing process of atrophy, persisting up to one year in all muscle grossly still recognizable as such. Under similar circumstances muscle subject to tenotomy exhibited no fibrillation. It is concluded, therefore, that with respect to the time course fibrillation may underlie the atrophy of denervated muscle but that it cannot be held accountable for the atrophy of tenotomy. An alternative explanation is offered for the atrophy in the latter condition.

12. Rehn, E.: Electrophysiologie krankhaftveränderten menschlichen Muskeln, Deutsche Ztschr. f. Chir. **162**:155, 1921.

13. Davenport, H. K., and Ranson, S. W.: Contracture Resulting from Tenotomy, Arch. Surg. **21**:995 (Dec., pt. 1) 1930.

14. Harding, A. E. B.: Arthritic Muscular Atrophy: The Oxygen Consumption of Atrophied Muscles, J. Path. & Bact. **29**:189, 1926.

15. Lorenz, H.: Die Muskelerkrankungen, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1904, vol. 11, pt. 3, p. 1.

POSTHERPETIC NEURALGIA IN THE DISTRIBUTION OF THE CRANIAL NERVES

EVIDENCE FOR SYMPATHETIC MEDIATION AND SURGICAL CURE

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The type of neuralgia which occasionally follows herpes zoster has been, so far as I am aware, almost intractable to treatment. Bailey [1] expressed the belief that the pain is not susceptible to surgical relief. This author and others—Craig,[2] Frazier [3] and Peet [4]—have asserted that the responsible lesion must be central.

That the major pathologic changes in herpes zoster exist in the cerebrospinal ganglia has been clearly demonstrated by Head and Campbell [5] and others. Consequently, since a major lesion is known to exist in the gasserian ganglion after zoster of trigeminal distribution, it has seemed incredible that section of the fifth sensory root would not abolish the pain.

I, as well as others (Harris [6]), have relieved postherpetic neuralgia in the distribution of one or more spinal nerves by section of posterior roots, but two or three roots above and below the distribution involved must also be sectioned.

With zoster involving the distribution below the neck, it is not surprising that high chordotomy will relieve the pain. Such has been the case in my experience with 1 patient.

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1. Bailey, P.: Neuralgias of the Cranial Nerves, S. Clin. North America **11**: 61-77, 1931.

2. Craig, W. McK.: Typical and Atypical Neuralgia of the Face and Neck, Proc. Staff Meet., Mayo Clin. **2**:677-681, 1936.

3. Frazier, C. H.: Neuralgias of the Trigeminal Tract and Facial Neuralgias of Other Origin: Impressions Derived from a Survey of Five Hundred and Fifty-Five Cases, Ann. Otol., Rhin. & Laryng. **30**:855-869, 1921.

4. Peet, M. M.: Postherpetic Trigeminal Neuralgia: Persistence of Pain After Section of the Sensory Roots of the Gasserian Ganglion, J. A. M. A. **92**: 1503-1505 (May 4) 1929.

5. Head, H., and Campbell, A. W.: The Pathology of Herpes Zoster and Its Bearing on Sensory Localization, Brain **23**:353-523, 1900.

6. Harris, W.: Neuritis and Neuralgia, London, Oxford University Press, 1926.

Putnam [7] failed to relieve the pain of severe neuralgia by chordotomy in 2 cases. He expressed the opinion, however, that there was a psychic element in both. The neuralgia in 1 case was in the distribution of the second thoracic nerve.

Neuralgia in the distribution of a cranial nerve, however, has been most baffling. Peet [4] reported 2 cases of postherpetic neuralgia in the ophthalmic distribution of the trigeminal nerve. Complete division of the sensory root of this nerve failed to eliminate the pain. On the other hand, Harris [8] stated:

> For this, alcoholic injection of the Gasserian ganglion may give complete relief, and I have done this in three such cases, but it is necessary to produce total and lasting anesthesia equal to that resulting from a gasserectomy.

The evidence gleaned from the literature concerning this as well as other forms of atypical neuralgia of the face involving trigeminal distribution indicates a great difference in results of treatment, depending on whether injection into the ganglion or division of the root is done.

Frazier [3] must have been aware of this difference when he stated:

> Theoretically one might assume that, of all forms of neuralgia, the radical operation on the sensory root would be particularly appropriate in those of herpetic origin, where the lesion is believed to be in the ganglion. There are reasons, which I will not here go into, questioning the soundness of this seemingly logical deduction, and on that account I recommend for my patient an alcoholic injection rather than the major operation.

I have been unable to find further reference to what Frazier had in mind.

So far as I am aware, no one has expressed the idea that postherpetic neuralgia is mediated by afferent sympathetic [9] fibers and hence may be eliminated by removal of the stellate and upper two or three thoracic sympathetic ganglia.

The recent literature [10] has overwhelmingly borne out the theory that all the afferent sympathetic fibers of at least the scalp, face and neck enter the central nervous system at or below the first thoracic segment.

I report 3 cases of postherpetic neuralgia of the head and neck, the surgical results in which show that the pain is mediated by fibers that may be called afferent sympathetic and indicate in a general way the course of these fibers, as well as the fact that the pain may be cured by stellate and upper thoracic ganglionectomy.

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7. Putnam, T. J.: Personal communication to the author.

8. Harris, W.: Persistent Pain in Lesions of the Peripheral and Central Nervous System, Brit. M. J. **2**:896-900, 1921.

9. "Sympathetic" is used here with reference to the thoracolumbar system and in contradistinction to the parasympathetic system. I use the term "afferent sympathetic" advisedly and intend that it have the same meaning as "viscerosensory," the term used by White.[10]

10. White, J. C.: The Autonomic Nervous System: Anatomy, Physiology and Surgical Treatment, New York, The Macmillan Company, 1935, p. 108.

REPORT OF CASES

CASE 1.—*History.*—G. E., a white man aged 74, was referred by Dr. E. M. Wiles, of Des Moines, Iowa, on March 29, 1938. He complained of severe pain in the left eye and on the left side of the nose and forehead. He had an attack of "shingles" in February 1937, which he located in the distribution of the ophthalmic division of the left trigeminal nerve. At that time he was seized with severe pain on the top of the head, which continued until blisters appeared three days later. Then a different type of pain and, for the first time, sensitiveness of the skin developed and remained severe until the time of examination. The pain was continuous, with exacerbations of greater severity, throbbing and shooting and a sensation as if "some one were sticking needles in the skin." Changes in temperature, wind and touch caused severe, electric, spreading pain, and the patient had elicited two very tender points—one on the side of the nose and one at the supraorbital notch.

The past and the family history were unessential.

Examination.—General: The temperature was 98 F., the pulse rate 80, the respiratory rate 20 and the blood pressure 165 systolic and 90 diastolic. Examination of the blood and urine gave normal results. There were moderate arteriosclerosis, premature cardiac beats and a hydrocele on the left side.

Neurologic: There was ptosis of the left eyelid, and the left pupil was pinpoint size and fixed. Trophic changes in the skin following the herpes zoster were definite and outlined accurately the accepted ophthalmic distribution of the fifth nerve. Sensitiveness to pinprick was 50 per cent normal, and, as nearly as could be told, that to touch was similar, but touch, light brushing or blowing produced a severe pain, which spread over the entire area involved (fig. 1). Flicking the eyebrow or hair over the forehead caused pain, and the skin over the bridge of the nose on the left appeared to be an especially sensitive trigger zone. Tears flowed constantly from the left eye, which was held partly closed because it was sensitive to light.

First Procedure.—In order to test the probable efficacy of section of the fifth root, a large wheal was raised under the eyebrow with procaine hydrochloride. The forehead above this became completely insensitive. The intern suggested shaving the patient at this time in preparation for section of the fifth root, and this was done without the slightest discomfort. I believe it would otherwise have been almost impossible.

First Operation.—The sensory root of the fifth nerve on the left was sectioned by the subtemporal route. A small filament was spared at the most inferior aspect of the root in the hope that some sensation would be left in the mandibular division.

The pain was not influenced by this procedure. On examination, Dr. Clarence Van Epps recorded that sensation to pinprick and cotton was preserved from 25 to 50 per cent over the forehead and upper part of the cheek and was absent on the chin. From repeated examinations I was convinced that the patient's answers indicated that stimulation provoked acquired sympathetic pain and not somatic sensation. I believe that the anesthesia of the mandibular region indicated that sensory function of the fifth nerve had been completely eliminated.

Postoperative herpes appeared in the maxillary region.

Second Operation.—Since local anesthesia of the supraorbital nerve was so successful, why had section of the sensory root of the fifth nerve failed? A logical answer is that the supraorbital vessels had also been anesthetized or that certain fibers in the peripheral part of the fifth nerve do not reach the central nervous system through the root of the nerve.

Without any anesthesia, an incision was made the length of the eyebrow. The patient did not feel the incision through the skin, but when muscle was encountered he complained bitterly, particularly when even the tiniest vessels were cut. When the supraorbital artery was mobilized, he, though a very cooperative patient, threatened to get off the table. Severe pain accompanied its section, and stimulation of the proximal end with very weak faradic current was equally as painful. The same findings held true for the supraorbital nerve. It was then necessary to inject a little procaine in the muscle to carry the incision to the bone. The periosteum, like the skin, was insensitive to a sharp cut. Everything beneath the eyebrow having been divided, the wound was closed.

The forehead remained anesthetic and free from pain, but the hyperesthesia of the eye and nose was not influenced. Two weeks later there was slight hyper-

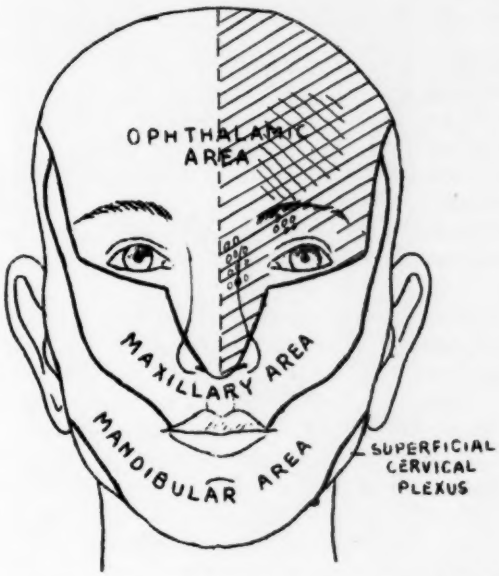

Fig. 1 (case 1).—In the area of single hatching punctiform touch sensation was about 75 to 50 per cent of normal. Sensation to pinprick was about 50 per cent of normal. Two points were not discriminated when less than 9 cm. apart (points 2 cm. apart were correctly discriminated on the right). Heat was not sensed. Cold was distinguishable, though much less than on the right. Deep pressure was not painful, but light stroking with cotton or flicking the eyebrow or the hair over forehead caused spreading, electric-like pain over the area of hatching.

The area of double hatching represents that totally anesthetic to punctiform stimuli.

Small circles represent specially sensitive trigger zones.

esthesia as one dragged a toothpick across the peripheral margin of the ophthalmic zone to the temple, and also at the midsagittal plane of the forehead.

At the time of writing (nine months later) the forehead is still free from pain, but the maxillary and mandibular regions have grown hypersensitive (information by letter).

I believe that these results indicate that this patient's postherpetic neuralgic pain is mediated by visceral afferent fibers. These afferent fibers course in the walls of vessels and also in company with peripheral nerve trunks, but they do not follow the sensory root of the trigeminal nerve into the central nervous system.

The herpes zoster, through some mechanism, has caused these afferent sympathetic fibers to become markedly hypersensitive, at least so far as the mediation of their impulses to consciousness is concerned.

The subsequent spread of hypersensitivity to the mandibular and maxillary regions is interesting and indicates that when the mechanism of neuralgia is established in one zone of the fifth nerve, abolition of somatic sensibility in another zone by section of the sensory root may cause spread of the neuralgic pain. Peet [4] has had a similar experience.

Case 2.—*History.*—F. P., a white man aged 76, referred by Dr. E. E. Blythe, of Riverside, Iowa, in May 1938, complained of severe, constant pain over the left side of the forehead and in the eye socket. Three days before reference he had been seized suddenly with stinging pain over the left eye. The pain continued, and four days later, when he was in the ward, small blisters appeared over the region corresponding to the ophthalmic division of the left trigeminal nerve. Pain continued in this region, there being exacerbations of greater severity from time to time. He described the location of maximum pain as the eye socket and behind the eyeball.

Treatment.—The left eye was kept dilated with scopolamine and cocaine for a time. The patient was given a full course of injections of typhoid vaccine and radiation, amounting to 1,600 roentgen units, directed to the left gasserian ganglion. He derived no relief from this treatment. He was discharged, but returned to the hospital two months later (July), complaining bitterly.

Examination.—Aside from the local condition, general and neurologic examination gave normal results except for a degree of auricular fibrillation and arteriosclerosis. Laboratory examination, including a Wassermann test, gave normal results.

There was diffuse scarring, which outlined accurately the distribution of the left ophthalmic division (fig. 2). Sensation to punctiform pain and touch was absent above the eye and was about 75 per cent normal just below the eye. Dragging a toothpick over the affected area caused a spreading, unpleasant pain, but not as marked as that in case 1. The eyebrow and lashes were scanty on the left. The lid on this side was slightly ptosed. The pupils were equal, but slightly irregular, and reacted sluggishly to light. The corneal reflex was absent on the left.

First Operation.—Having deduced from my experience in case 1 that pain of this type is mediated by sympathetic afferent fibers, or at least by fibers many of which course in the walls of vessels, I thought section of the external carotid artery was justified. In view of the arteriosclerosis, I considered this procedure more advisable than an attempt to strip the common carotid artery. On July 15 the left external carotid artery was divided, and the left superior cervical ganglion was removed entirely. This procedure did the patient neither harm nor good. When I approached him the next day he gave me a forlorn look and shook his head.

The superior cervical ganglion was studied in sections prepared with hematoxylin and eosin and Held's and Nissl's stains. No pathologic changes were demonstrable.

Second Operation.—From my own experience and that of others, I knew that section of the sensory root of the trigeminal nerve would be a futile procedure. However, the benefits that have been reported to follow injections into the gasserian ganglion led me to suspect that there must be some difference in the two procedures based on physiologic grounds. If it is true that pain-bearing fibers reach the ganglion but leave it by some route other than its sensory root, a section of the peripheral branches just distal to the ganglion should prove beneficial.

Consequently, on July 27, through a subtemporal exposure, the ophthalmic and maxillary divisions were completely sectioned just distal to the ganglion,

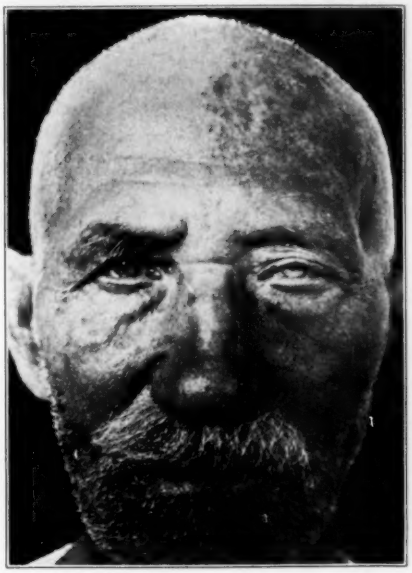

Fig. 2 (case 2).—Photograph showing the postherpetic scarring which outlined accurately the distribution of the left ophthalmic division.

leaving the mandibular division intact. It should be added that in cauterizing a small bleeding vessel I inadvertently seared the adventitia of the ophthalmic artery, but not sufficiently to occlude it.

Result.—When I approached the patient on the next day, he appeared very happy and grasped my hand. He stated that the severe pain in and behind the eyeball was gone. There was evidence of paralysis of the left sixth nerve.

The patient is free from pain at the time of writing (six months). The paralysis of the sixth nerve has persisted.

CASE 3.—*History.*—S. J., a white man aged 65, referred by Dr. B. L. Basinger, of Goldfield, Iowa, in July 1938, complained of pain in the left side of the face, neck and throat, the left shoulder and arm and the left side of the chest. In October 1937 (thirteen months before), there had developed hyperesthesia of the skin in front of the left ear. This spread to involve the left side of the occiput,

the left ear, the left side of the neck, the left shoulder and arm and the anterior aspect of the chest to the breast. Three days later these areas became red and swollen, and blisters appeared. For about one month the pain was intense, and the patient was unable to bear the slightest pressure on the zones involved. The vesicles on the chest appeared to follow the distribution of the first and second dorsal nerves on the left. Pain and hyperesthesia did not involve the right side.

After this episode the patient noticed that his hearing in the left ear was not good, and he was dizzy at times, particularly when lying on the right side.

Examination.—General examination gave essentially normal results except for moderately advanced arteriosclerosis. The blood pressure was 125 systolic and 80 diastolic. The blood and urine were normal, and the Wassermann reaction of the blood was negative.

Neurologic examination revealed the following abnormalities: There was scarring of the skin over the left side of the face, neck and shoulder, similar to that which follows herpes zoster. Sensitiveness to punctiform pain and touch stimuli was estimated to be about 25 per cent of normal over the left side of the neck and shaded off to 80 per cent of normal over the left temple. Pain and touch sensations also shaded off to 90 per cent of normal at a line about 2 inches (5 cm.) below the clavicle. The patient complained of a spreading, unpleasant pain when any of these zones, including the left side of the breast and the left arm, were brushed with the fingers. Brushing the zones just in front of and behind the ear and light rubbing of the pinna between the fingers were especially painful. He could not tolerate the insertion of the end of one's finger into the external auditory meatus. Tender pressure points were elicited over the temporal, occipital and carotid arteries. He also complained of severe pain referred to the left ear drum on swallowing. All hypersensitive zones on the left were sharply delimited by the midsagittal plane.

Diagnosis.—The diagnosis was neuralgia following herpes zoster, which had attacked the fifth, seventh and ninth cranial nerves, all the cervical nerves on the left and the left first and second dorsal nerves. Evidently, the lesion of the geniculate ganglion had involved the eighth nerve, as evidenced by diminution of auditory acuity on that side and dizziness. The motor facial nerve, however, had escaped injury.

First Operation.—Through a left lateral postperitoneal approach, the splanchnic nerves were severed as they enter the abdominal cavity, and the first and second lumbar ganglia were removed. In a number of cases of essential hypertension of advanced grade, in my experience, headache had been consistently relieved by sp'anchnectomy to a remarkable degree. The patients have volunteered this information, and in cases in which the procedure has had no influence on the blood pressure the patients have stated that it was worth while in view of the relief from headache. There seemed to be a subjective sense of well-being accompanying the relief of headache.

In view of the possibility that all sympathetic afferent fibers from the head and neck may take a devious route down the great vessels and enter the central nervous system through the splanchnic nerves, the first operation on this patient was splanchnectomy.

Result.—All hyperesthesia of the skin from the clavicle down, including that of the breast and arm, was definitely relieved. No longer was spreading pain referred to these zones. The situation above the clavicle remained as before.

Second Operation.—The left stellate and the three upper thoracic sympathetic ganglia were removed. As the stellate ganglion appeared to comprise a fusion of

the inferior cervical and the first thoracic ganglion, it is probable that four dorsal ganglia were removed.

Result.—The patient was completely relieved of all pain and hyperesthesia. Swallowing was no longer painful. The ear and great vessels were no longer tender. He has remained completely free from this neuralgia to the time of writing (five months), and on check-up examination he demonstrated that he could shake his head from side to side and use his left arm and hand freely, movements which had been restricted before operation because of pain.

The results in this case again bear out the proposition that the pain of postherpetic neuralgia is mediated by afferent sympathetic fibers and that such pain involving the head and neck may be relieved by removal of the stellate and upper thoracic ganglia. It may not be necessary to remove as many thoracic ganglia as was done in this case.

It is interesting that left splanchnectomy relieved the hyperesthesia of the arm and breast. This may indicate that some of the afferent sympathetic fibers from the arm course down the great vessels in the chest and enter the sympathetic system by way of the splanchnic nerves.

It seems probable that many afferent fibers from the intracranial vessels course in this manner. However, this does not mean that section of the splanchnic nerves is necessary to obliterate such fibers. It is likely that, after entering the sympathetic chain, they course upward for the most part to the stellate and upper thoracic ganglia before entering the cord by way of the posterior roots. Hence, one can correlate the relief of headache by splanchnectomy with the relief obtained by stellate and upper thoracic ganglionectomy. Love and Adson,[11] for example, in a review of their cases of stellate and upper thoracic ganglionectomy, reported that 75 per cent of patients were relieved partially or completely of headaches.

SUMMARY

Three cases of postherpetic neuralgia involving the head are reported. Surgical therapy was instituted, the results of which indicate that: (1) the pain of postherpetic neuralgia is mediated by afferent sympathetic fibers; (2) these fibers course in company with vessels and nerve trunks, but all ultimately enter the central nervous system at or below the first thoracic segment; (3) the neuralgia when involving the head and neck may be cured by removal of the stellate and upper first few (possibly only two or three) thoracic sympathetic ganglia on the ipsilateral side.

In case 1, one of neuralgia in the distribution of the ophthalmic division of the trigeminal nerve, pain and hyperesthesia above the eyebrow were completely relieved after cocainization or section of the supraorbital

11. Love, J. G., and Adson, A. W.: Effect of Cervicothoracic Sympathectomy on Headaches, Arch. Neurol. & Psychiat. **35**:1203-1207 (June) 1936.

nerve and artery. After section of the sensory root of the fifth cranial nerve, both these structures were exceedingly painful to mechanical and electrical stimulation.

In case 2, also one of neuralgia involving the distribution of the ophthalmic nerve, severe, constant pain in the eye socket was completely relieved by section of the ophthalmic and maxillary nerves just distal to the gasserian ganglion. This bears out the proposition, as indicated in the literature, that there is a significant physiologic difference in sectioning the sensory root of the fifth nerve and in destroying the ganglion or cutting the major branches just distal to the ganglion. The probable explanation is that some sympathetic afferent fibers course by way of the ganglion, as is known to be the case with the sphenopalatine ganglion, but do not enter the central nervous system by way of the sensory root of the fifth nerve.

In case 3 neuralgia involved the distribution of the fifth, the sensory portion of the seventh and the ninth cranial nerve, all the cervical nerves on one side and the first and second thoracic nerves on the same side. Pain and hyperesthesia of the upper part of the chest and arm disappeared after homolateral splanchnectomy. Complete relief of the neuralgia of the face, occiput, ear and neck, which constitutes complete cure, was obtained after removal of the homolateral stellate and upper four thoracic sympathetic ganglia. Probably fewer, if any, thoracic ganglia need be removed.

The irregular results and partial relief of various atypical neuralgias of the face and scalp obtained by procedures such as injection into the sphenopalatine or gasserian ganglia or periarterial sympathectomy may be attributable to the obliteration of varying numbers of afferent sympathetic fibers.

It appears, however, that all these afferent fibers, at least the extracranial, ultimately reach the stellate and upper thoracic ganglia before entering the central nervous system. Hence, removal of these ganglia completely desympathectomizes the face, scalp and neck on the ipsilateral side.

CONCLUSIONS

1. The pain and hyperesthesia of postherpetic neuralgia are mediated by afferent sympathetic nerves.

2. When the neuralgia involves the head or neck it may be eliminated by removal of the stellate and several upper thoracic sympathetic ganglia on the ipsilateral side.

INFLUENCE OF FEAR, PHARMACOLOGIC ACTION AND CONVULSION IN METRAZOL THERAPY

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AND

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Three main factors, either singly or in combination, have been held responsible for the therapeutic results obtained with metrazol treatment of psychotic patients: (1) the convulsion, (2) the pharmacologic effect of the drug and (3) the fear reaction. In the present study it was attempted to isolate the emotional and pharmacologic reactions and to investigate their effects on the blood pressure, pulse, respiration, leukocytes and various chemical constituents of the blood.

MATERIAL AND METHOD

Seventeen patients (12 men and 5 women) who were receiving a course of metrazol treatment were studied. Their ages ranged from 15 to 44; the average age was 28.3. In 9 of the cases the disease was classified as schizophrenia; in 6, as manic-depressive psychosis; in 1, as a primary behavior disorder, and in 1, as a traumatic psychosis.

Six of the patients, during the second, third or fourth week of treatment, were given a dose of metrazol which on the previous day of treatment had resulted in a convulsion. The injection was made slowly, however, so that a convulsion did not take place. None of the 6 patients were known to have exhibited marked fear of the treatment. The remaining 11 patients, each on a separate day, were prepared for the treatment as on previous occasions. However, physiologic solution of sodium chloride, instead of metrazol, was injected. The bottle from which the solution was drawn was marked in exactly the same way as the one containing metrazol. Special care was taken to keep even the nurses in ignorance of the change. Seven of the 11 patients were known to have exhibited marked fear of the treatment.

The blood pressure, pulse rate and respiratory rate were recorded, and a sample of blood was drawn from the cubital vein. The solution of sodium chloride or metrazol was then injected. The vital signs were registered every five minutes during the first half hour after injection, every ten minutes during the following hour and every thirty minutes for another hour and a half. In addition, a sample of blood was collected ten minutes, one hour and two hours, respectively, after the injection. The p_H and the carbon dioxide, calcium and dextrose contents of the serum were determined, and leukocyte counts were made.

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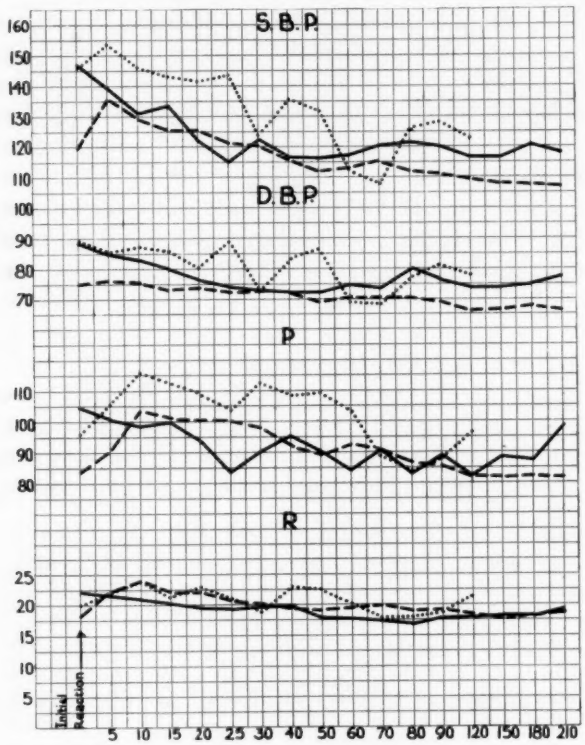
VITAL SIGNS

In the chart are recorded the systolic and diastolic blood pressure, and the pulse and respiratory rates. The heavy line plots the reactions of the 11 patients who were given injections of physiologic solution of sodium chloride; the broken line, those of the 6 patients who were given metrazol intravenously without production of a convulsion. The dotted line represents the reactions of 10 patients, previously studied,[1] who



Average values for systolic rate (*S. B. P.*) and diastolic (*D. B. P.*) blood pressures, pulse rate (*P*) and respiratory rate (*R*) in three groups of patients treated with physiologic solution of sodium chloride and convulsive and subconvulsive doses of metrazol, respectively.

In this chart, the reactions of patients given physiologic solution of sodium chloride are represented by a solid line; those of patients given metrazol without convulsions by a broken line, and those of patients given metrazol with convulsions by a line of dots.

1. Low, A. A.; Sonenthal, I. R.; Blaurock, M. F.; Kaplan, M., and Sherman, I.: Metrazol Shock Treatment of the "Functional" Psychoses, Arch. Neurol. & Psychiat. **39**:717 (April) 1938.

received injections of metrazol with the production of convulsions. The chart shows that the injection of metrazol if followed by a convulsion produces stronger effects on the systolic and diastolic blood pressures and the pulse and respiratory rates than either the injection of metrazol without convulsion or the injection of physiologic solution of sodium chloride. The initial rates were consistently lower for the group of 6 patients treated with metrazol without convulsions. The relative absence of fear, in all likelihood, accounts for the lower rates.

Mean Values for the p_H, Carbon Dioxide, Dextrose, Calcium and Leukocytes of the Blood Before and After Injection of Metrazol in Convulsive or Subconvulsive Doses or of Physiologic Solution of Sodium Chloride

		Patients Given Injections of Metrazol		Patients Given Injections of Physiologic Solution of Sodium Chloride
		With Convulsion	Without Convulsion	
p_H	Fasting	7.34	7.39	7.36
	After 10 min.	7.17	7.38	7.34
	After 1 hr.	7.29	7.43	7.35
	After 2 hr.	7.32	7.42	7.36
Carbon dioxide, vols. %	Fasting	57.5	57.3	57.5
	After 10 min.	34.1	50.5	55.8
	After 1 hr.	47.1	57.5	58.2
	After 2 hr.	56.4	57.3	57.3
Dextrose, mg. per 100 cc.	Fasting	73.4	98.1	107.5
	After 10 min.	90.9	111.0	110.1
	After 1 hr.	81.1	97.8	107.7
	After 2 hr.	72.7	98.5	97.6
Calcium, mg. per 100 cc.	Fasting	10.6	9.7	9.2
	After 10 min.	8.8	9.7	9.2
	After 1 hr.	9.2	9.6	9.6
	After 2 hr.	9.4	9.6	9.5
White blood corpuscles, thousands per cu. mm.	Fasting	7.145	9.825	10.378
	After 10 min.	11.767	11.070	10.977
	After 1 hr.	8.533	9.380	9.832
	After 2 hr.	8.170	10.130	9.527
Polymorphonuclear cells	Fasting	69.7	57.5	66.0
	After 10 min.	56.1	58.3	63.9
	After 1 hr.	65.3	67.1	69.5
	After 2 hr.	74.0	69.5	69.9
Lymphocytes	Fasting	29.5	41.2	33.0
	After 10 min.	42.9	41.5	35.0
	After 1 hr.	33.9	32.0	29.4
	After 2 hr.	25.3	30.5	29.5

The table gives the mean values for the p_H, carbon dioxide, dextrose, calcium and leukocytes of the blood before and after injection, both for the patients who received injections of metrazol and for those who were given physiologic solution of sodium chloride. The values for the patients who had convulsions were again taken from the previously reported study.[1] It is obvious from the table that neither the physiologic solution of sodium chloride nor the metrazol without subsequent convulsion had any noticeable effect on the p_H and carbon dioxide content, while the metrazol if followed by a convulsion produced a marked drop in the p_H in the ten minute and one hour samples and in the carbon dioxide in the ten minute sample.

COMMENT

In 11 patients who received physiologic solution of sodium chloride the action of both the convulsion and the drug was eliminated. It is probable that fear was operative to a considerable extent. In 6 patients who were given a slow injection of metrazol, without production of a convulsion, the paroxysm was eliminated and the fear reaction reduced through proper selection of the patients. In 10 patients in whom convulsions were produced none of the factors—the paroxysm, the drug or the emotional reaction—was eliminated. The study indicates that the effect on the vital signs is most marked when a convulsion occurs; further, that the convulsion alone produces a fall in the p_H and the carbon dioxide content to acidotic levels. The inference seems permissible that both the marked rise in blood pressure and pulse rate and the significant fall in the p_H and carbon dioxide content observed in the course of a metrazol paroxysm are the result of the convulsion rather than of either the emotional or the pharmacologic reaction. Whether the therapeutic results are also due exclusively to the convulsion cannot be decided on the basis of this study.

CONCLUSIONS

1. To three groups of patients were given, respectively: (1) an injection of metrazol, with resultant convulsion; (2) an injection of metrazol, without convulsion, and (3) injections of physiologic solution of sodium chloride.

2. Marked effects on the vital signs and on the p_H and carbon dioxide content of the blood were not secured unless a convulsion occurred.

EFFECT OF PROLONGED INSULIN HYPOGLYCEMIA ON DISTRIBUTION OF WATER AND ELECTROLYTES IN BRAIN AND IN MUSCLE

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It has been suggested that convulsions in epilepsy [1] and during insulin hypoglycemia [2] may be influenced by varying body hydration. It has therefore been inferred that the disturbances in the distribution of water in the brain may be responsible for the convulsive phenomena. The present widespread employment of convulsant doses of insulin in the treatment of psychotic disorders has made timely the experimental investigation of the distribution of water in the brain following the administration of insulin. The purpose of the present communication is to present the results of the chemical analyses of the brains from normal cats and those given injections of insulin from which, by appropriate calculations, the distribution of water and electrolytes could be estimated. We have also included the results of the analyses of muscle from these animals, since this tissue represents the largest depot of water in the body.

PROCEDURE AND METHODS

Cats weighing between 2 and 3.5 Kg. were used as the experimental animals. Since their nutritional status was unknown prior to their delivery to the laboratory, they were kept for one week on an adequate diet of canned fish and milk before being studied. Prior to the removal of blood and tissue for chemical analyses, the animals were anesthetized with pentobarbital sodium (30 mg. per kilogram of body weight, intraperitoneally). Our preliminary work had shown that no significant changes in the distribution of water or electrolytes in brain or muscle were produced by this procedure. Blood was removed by cardiac puncture, after

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This study was aided by a grant from the Child Neurology Research Fund (Friedsam Foundation) and the Fluid Research Fund, Yale University.

1. (*a*) Fay, T.: Some Factors in the Mechanical Theory of Epilepsy, with Especial Reference to the Influence of Fluid and Its Control in the Treatment of Certain Cases, Am. J. Psychiat. **8**:783, 1929. (*b*) McQuarrie, I.: Epilepsy in Children: The Relationship of Water Balance to the Occurrence of Seizures, Am. J. Dis. Child. **38**:451 (Sept.) 1929.

2. Drabkin, D. L., and Ravdin, I. S.: The Mechanism of Convulsions in Insulin Hypoglycemia, Am. J. Physiol. **118**:174, 1937.

which the animals were killed by severing the great vessels at the base of the heart. The blood for analyses was collected under oil and allowed to clot, and the serum was removed in the usual manner. The brain was exposed after stripping the dura, and both hemispheres were removed for chemical analysis and histologic study. The cerebellum and upper part of the cord were also removed for pathologic investigations. Muscle, obtained from the hindlimbs, was dissected as free of fat as possible before analysis.

The methods for blood and tissue analyses have been described in a previous paper.[3] One change, however, should be noted. For determinations of tissue chloride the dried and pulverized material was suspended in a measured amount of water and allowed to stand in a securely stoppered container overnight. An aliquot was removed after centrifugation and total chloride determined by the method of Van Slyke and Sendroy.[4] The values for nonlipoid nitrogen in the brain represent the difference between total nitrogen and lipoid nitrogen, the latter being determined by analysis of the purified petroleum benzine (petroleum ether) extract. Values for nonlipoid phosphorus were determined by difference similarly. Blood sugar was determined by the Shaffer-Hartmann-Somogyi copper titration method[5] or the Folin ferricyanide colorimetric method.[6] The estimations of extracellular and intracellular water and the concentration of intracellular nitrogen, potassium and phosphorus were carried out as described by Harrison, Darrow and Yannet.[7] The statistical methods are those described by Dunn.[8]

The insulin[9] was injected subcutaneously in doses varying from 5 to 20 units per kilogram, about eighteen hours after the food remaining from the previous feeding was removed from the cages.

RESULTS

The results of the chemical analyses of the brains of 57 animals are presented. The animals were divided into four groups. Group 1 includes 20 normal animals and represents the controls for nutritional status and methods of anesthesia used. Five of these animals were allowed to remain under the effect of pentobarbital sodium for approximately from six to ten hours, no significant differences being noted in the distribution of water or electrolytes in the brain or muscle between this group and animals killed after much shorter periods of anesthesia. Animals

3. Yannet, H., and Darrow, D. C.: Effect of Hyperthermia on the Distribution of Water and Electrolytes in Brain, Muscle and Liver, J. Clin. Investigation **18**: 87, 1938.

4. Van Slyke, D. D., and Sendroy, J., Jr.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

5. Somogyi, M.: Notes on Sugar Determination, J. Biol. Chem. **70**:599, 1926.

6. Folin, O.: Supplementary Note on the New Ferricyanide Method for Blood Sugar, J. Biol. Chem. **81**:231, 1929.

7. Harrison, H. E.; Darrow, D. C., and Yannet, H.: The Total Electrolyte Content of Animals and Its Probable Relation to the Distribution of Body Water, J. Biol. Chem. **113**:515, 1936.

8. Dunn, H. L.: Application of Statistical Methods in Physiology, Physiol. Rev. **9**:275, 1929.

9. The insulin, in unmodified form, was furnished by Eli Lilly & Co., Indianapolis.

kept for varying periods (up to ten days) without food or water also failed to show significant changes in the brain and muscle.

The remaining 37 animals were studied during the various phases of insulin hypoglycemia. Fifteen animals (group 2) were killed from two to six hours after the injection of insulin. This group represents: (1) animals just prior to the convulsive seizures, when the respirations had become rapid and the animal either lay quietly or seemed agitated; (2) animals having convulsive seizures of varying intensity and salivating profusely; (3) animals that had passed from the convulsive stage into one of deep shock with hypothermia and were unresponsive to sensory stimuli of various kinds. The blood sugar in all these animals was always below 30 mg. per hundred cubic centimeters, and most often below 15 mg. per hundred cubic centimeters. Since analysis of the individual data for the animals in the various clinical states just described showed so little variation, it was thought profitable to include them all in one group (group 2).

Groups 3 and 4 represent 22 animals which received from 10 to 20 units of insulin per kilogram, were allowed to recover spontaneously and were killed from twenty-four to thirty hours after the injections of insulin. The blood sugar in all animals at this time was within normal limits. Of these, 12 animals (group 3) showed no demonstrable clinical evidence of any involvement of the central nervous system. Except for muscular weakness, they behaved like normal cats. Gait, reflexes and response to sensory stimuli showed no obvious impairment. Histologic examination of the brains of these animals showed no significant changes from the normal.

The remaining 10 animals (group 4) proved to be the most interesting of the entire series. All received from 15 to 20 units of insulin per kilogram of body weight. When examined approximately twenty-four hours after the injection of insulin, they all showed striking clinical evidence of widespread cerebral damage. The most appropriate descriptive term that could be applied to the clinical picture was that of "decerebrate rigidity." The animals were completely out of touch with the environment; they were insensitive to painful stimuli, such as pinprick or pinching the tail or extremity. Both forelegs and hindlegs showed resistance to passive flexion or extension. The "righting" reflex was absent or impaired, as was the "paw-lifting" reflex, which normally manifests itself when the animal is brought into contact with a table top while the legs are below the level of the surface. The knee jerks could be obtained without difficulty. The pupils reacted to light in the normal fashion. Attempts to walk produced an irregular, ataxic gait in some instances, but more often led merely to circling movements of the body around one foreleg as the pivot, while the animal remained on its side. Histologically, the brains of these animals showed widespread damage to the ganglion cells of the cortex, basal ganglia and upper part of the medulla. A detailed description of these changes will appear in another publication.[10]

The frequency with which the preceding clinical syndrome may be obtained is suggested by the following data. Thirty-six animals were given injections of from 10 to 20 units of insulin per kilogram during the course of these experiments. At the end of twenty-four hours 10 animals had died and 26 had survived. Of the latter group, 12 animals showed no demonstrable clinical evidence of involvement of the central nervous system, while 14 animals showed evidence of extensive damage to the brain. Four of the latter animals were observed one day longer.

10. Zimmerman, H. M., and Yannet, H.: The Histopathology of the Cerebral Changes Following Prolonged Insulin Hypoglycemia, to be published.

None of these animals took food or water, and they were found dead the following morning, or about forty-eight hours after the injection of insulin.

The results of the chemical analyses of the brains of the control and the experimental animals have been summarized in table 1. For purposes of comparison, the values are calculated on the basis of 1 Kg. of fat-free tissue. Column 1 gives the number of animals in each group. Columns 2 and 3 give the average concentrations of water and nonlipoid nitrogen, expressed in grams. Columns 4, 5, 6 and 7 give the average concentrations of chloride, sodium, potassium and nonlipoid phosphorus, expressed in millimols. The values included with the averages represent the standard errors. A difference between two means approximately equal to or greater than three times the standard error of the difference has been considered significant beyond the result of a chance sampling.

In group 2, the animals examined during the stage of hypoglycemia, there were no significant changes in the concentrations of water, nonlipoid nitrogen, potassium

TABLE 1.—*Average Content of Water, Nonlipoid Nitrogen, Chloride, Sodium, Potassium and Nonlipoid Phosphorus Per Kilogram of Fat-Free Brain of Control and of Experimental Animals*

(1) No. of Animals	(2) Water, Gm.	(3) Nonlipoid Nitrogen, Gm.	(4) Chloride, mM	(5) Sodium, mM	(6) Potassium, mM	(7) Nonlipoid Phosphorus, mM
			Group 1. Control Animals			
20	862 ± 1.1	16.4 ± 0.34	48.0 ± 0.70	61.2 ± 0.66	101 ± 0.73	68.8 ± 1.8
			Group 2. Animals During Hypoglycemic State			
15	857 ± 2.2	17.0 ± 0.13	44.7 ± 0.53	57.9 ± 0.87	102 ± 0.88	68.9 ± 2 2
			Group 3. Animals Which Survived with No Demonstrable Evidence of Involvement of Central Nervous System			
12	857 ± 2.4	17.3 ± 0.22	45.1 ± 1.6	63.4 ± 1.3	99.3 ± 1.8	74.9 ± 2.6
			Group 4. Animals Which Survived with Evidence of Involvement of Central Nervous System			
10	868 ± 2.8	16.7 ± 0.20	54.7 ± 2.1	77.9 ± 3.2	83.0 ± 2.4	61.2 ± 4.5

or nonlipoid phosphorus. There were, however, significant decreases in the concentrations of chloride and sodium. In this group, no significant difference could be found between the 8 animals that received less than 10 units of insulin per kilogram of body weight and the 7 animals that received from 10 to 20 units per kilogram.

In group 3, the animals that showed no obvious clinical evidence of involvement of the central nervous system, no significant differences in any of the constituents could be demonstrated.

In group 4, the animals that showed the striking evidences of damage to the central nervous system, significant increases in the concentrations of chloride and sodium and a decrease in the concentration of potassium occurred. The concentrations of water, nonlipoid nitrogen and phosphorus remained within normal limits.

It will be noted that the sum of the concentrations of sodium and of potassium was essentially unchanged in all the experimental groups.

Table 2 gives the concentrations of sodium, chloride and water in the serum of the control animals and of those given insulin. The values shown are the

averages and their standard errors. It will be noted that no significant differences in the concentrations of water, sodium or chloride existed between the control and the experimental groups. The concentrations of sodium in the serum and those of sodium plus potassium in the tissues represent, to a great extent, the most important factors controlling the maintenance of osmotic pressure in the body. The lack of change, therefore, in the concentration of extracellular sodium (as measured by its concentration in the serum) and in the concentrations of sodium plus potassium in the brain agrees with our conception of the maintenance of osmotic equilibrium. It follows that since the total water content of the brain remained unaffected, the changes found in the individual concentrations of sodium and of potassium in the brain in groups 2 and 4 must represent significant shifts of water and electrolytes between the brain cells and the extracellular fluid. In order to describe these changes more clearly, the chemical data given in table 1 were analyzed according to the procedures described by Harrison, Darrow and Yannet [7] and the results summarized in table 3. The calculations used were based on the

TABLE 2.—*Average Concentration of Sodium, Chloride and Water per Liter of Serum in Control and Experimental Animals*

No. of Animals	Sodium, mEq.	Chloride, mEq.	Water, Cc.
Group 1. Control Animals			
20	152 ± 1.0	118 ± 0.7	934 ± 2.0
Group 2. Animals During Hypoglycemic State			
15	152 ± 1.3	121 ± 1.3	928 ± 2.0
Group 3. Animals Which Survived with No Evidence of Involvement of Central Nervous System			
12	151 ± 1.0	116 ± 0.9	931 ± 1.8
Group 4. Animals Which Survived with Evidence of Involvement of Central Nervous System			
10	154 ± 1.8	118 ± 1.6	925 ± 2.2

assumption that all tissue chloride is extracellular. A discussion of the theoretic considerations involved in these calculations is given in the previous paper [7] and will not be repeated here. In table 3, columns 1 and 2 give the average percentages of extracellular and intracellular water; columns 3, 4 and 5 give the average concentrations per liter of intracellular water of nonlipoid nitrogen, potassium and nonlipoid phosphorus; column 6 gives the average ratio of potassium to nonlipoid nitrogen in the intracellular water, and column 7 (labeled "excess" sodium) gives the average quantity of sodium per kilogram of fat-free tissue not accounted for by that present in the extracellular water. The standard error is included with the average value in each instance.

In group 2 there were a significant decrease in extracellular water and a corresponding increase in intracellular water. Since there was no change in the total water content these changes must represent a shift of water from outside to inside the cell. This shift of water resulted in a slight dilution of the intracellular elements, which explains the decreases in the concentrations of intracellular nonlipoid nitrogen and potassium. The constancy of the ratio of potassium to nonlipoid nitrogen shows that the decrease in concentration of potassium was

not due to loss of intracellular potassium but was proportionate to the dilution of intracellular protein. Although there was a decrease in the average concentration of nonlipoid phosphorus, in line with the intracellular dilution, the scattering of the results makes the significance of this finding difficult to evaluate.

In group 3 there were no significant changes in the proportion of extracellular and intracellular water or in the concentration of intracellular nitrogen or phosphorus. The decrease in the concentration of intracellular potassium, however, seems to be significant. The pronounced decrease in the ratio of potassium to nonlipoid nitrogen, moreover, suggests that this decrease was due to actual loss of potassium from the cell.

In group 4 significant changes in the distribution of water and in the concentration of intracellular elements could be demonstrated. There can be noted

TABLE 3.—*Average Distribution of Water, Expressed in Percentages of Fat-Free Weight; Concentration of Nonlipoid Nitrogen, Potassium and Nonlipoid Phosphorus per Liter of Intracellular Water, and the Content of "Excess" Sodium Per Kilogram of Fat-Free Tissue in Brains of Control and of Experimental Animals*

(1) Extracellular Water, Percentage	(2) Intracellular Water, Percentage	(3) Intracellular Nonlipoid Nitrogen, Gm.	(4) Intracellular Potassium, mM	(5) Intracellular Nonlipoid Phosphorus, mM	(6) Potassium-Nitrogen Ratio	(7) "Excess" Sodium, mM
Group 1. Control Animals						
36.3 ± 0.42	49.9 ± 0.40	33.0 ± 0.30	198 ± 1.8	138 ± 3.4	6.03 ± 0.04	4.6 ± 0.14
Group 2. Animals During Hypoglycemic State						
32.9 ± 0.46	52.8 ± 0.42	32.0 ± 0.36	189 ± 1.9	132 ± 3.7	5.94 ± 0.05	6.3 ± 0.16
Group 3. Animals Which Survived with No Demonstrable Evidence of Involvement of Central Nervous System						
34.4 ± 1.3	51.3 ± 1.3	34.0 ± 0.90	192 ± 2.1	148 ± 4.6	5.68 ± 0.08	9.4 ± 0.42
Group 4. Animals Which Survived with Evidence of Involvement of Central Nervous System						
40.7 ± 1.3	46.1 ± 1.2	36.3 ± 0.80	178 ± 4.0	134 ± 9.3	4.92 ± 0.09	13.9 ± 0.56

an increase in the extracellular water associated with a corresponding decrease in intracellular water. Since the total water content was unchanged, this represents a shift of water from cells to extracellular spaces. This shift of water from the cells was accompanied by an increase in the concentration of intracellular nonlipoid nitrogen. It is also apparent that associated with the shift of water there occurred a loss of potassium from the cells, leading to marked reduction in the ratio of potassium to nonlipoid nitrogen. Little statistical significance can be given to the average value for intracellular nonlipoid phosphorus because of the wide scattering of the individual concentrations. The interpretation of the changes in "excess" sodium is at present problematic. This is necessarily so since it is not entirely clear what significance should be attributed to the "excess" sodium in the brains of the control animals. Two possibilities may be suggested. First, it represents sodium present in the cell as part of the cellular protoplasm, and second, it is part of the connective tissue–supporting structure, existing in non-

ionizable combinations similar to a large part of the sodium present in cartilage.[11] We favor the first possibility primarily because it was possible to demonstrate significant increases in "excess" sodium, especially in the brains of animals in groups 3 and 4, in which significant losses in cellular potassium took place. The increases in "excess" sodium, if one considers these as intracellular, almost entirely compensate for this loss, leaving the sum of sodium and potassium within the cell unchanged. This agrees with the absence of any significant changes in the concentration of sodium in the serum and fits better with our conception of osmotic equilibrium.

We may, then, summarize the changes in distribution of water and electrolytes in the brain during and following severe insulin hypoglycemia in the following manner:

1. During hypoglycemia there is a shift of water from the extracellular spaces into the cells, leading to a dilution of the intracellular contents.

2. Of the animals that survived the injection of a large dose of insulin, about half showed no demonstrable evidence of involvement of the central nervous system. Histologic examination of the brains of these animals revealed no significant pathologic changes. However, chemically it was possible to demonstrate a change in cellular composition, as shown by a significant loss of intracellular potassium.

3. The remaining animals that survived showed evidence of widespread cerebral damage. In these animals a marked loss of cellular water occurred, leading to shrinking of the cell and an increase in extracellular fluid. A proportionately greater loss of cellular potassium was demonstrated, resulting in a decrease in the concentration of intracellular potassium.

Changes of any appreciable degree in the distribution of water or electrolytes in the muscles as a result of insulin hypoglycemia could not be demonstrated. The summary of the results of the chemical studies and their analysis by the previously mentioned method of Harrison, Darrow and Yannet are given in tables 4 and 5. In these tables, groups 3 and 4 have been combined for convenience, since no essential differences were found between them. Table 4 gives the average content of water, nitrogen, chloride, sodium, potassium and phosphorus, calculated on the basis of 1 Kg. of fat-free muscle. A slight decrease in the chloride in group 2 can be noted; otherwise the changes are not significant. When the distribution of water and the concentrations of intracellular nitrogen, potassium and phosphorus are estimated (table 5), a slight decrease in the extracellular water and increase in the intracellular water are also noted in group 2. Although

11. Harrison, H. E.; The Sodium Content of Bone and Other Calcified Material, J. Biol. Chem. **120**:457, 1937.

the averages for the concentrations of intracellular nitrogen, potassium and phosphorus are lowered, suggesting a dilution effect, the differences are too small to be estimated accurately. A significant increase in "excess" sodium, which, as we previously suggested, probably represents intracellular sodium, can be noted in group 2. The probable shift of water and sodium into the muscle cell during muscular activity (in

TABLE 4.—*Average Content of Water, Nitrogen, Chloride, Sodium, Potassium and Phosphorus Per Kilogram of Fat-Free Muscle in Control and Experimental Animals*

(1) No. of Animals	(2) Water, Gm.	(3) Nitrogen, Gm.	(4) Chloride, mEq.	(5) Sodium, mEq.	(6) Potassium, mEq.	(7) Phosphorus, mM
			Group 1. Control Animals			
20	776 ± 2.0	34.6 ± 0.2	13.4 ± 0.4	18.3 ± 0.4	107 ± 0.7	75.3 ± 0.5
			Group 2. Animals During Hypoglycemic State			
15	775 ± 2.1	34.9 ± 0.4	11.5 ± 0.4	18.9 ± 0.6	107 ± 0.8	74.7 ± 0.6
			Groups 3 and 4. Animals Which Survived Severe Hypoglycemia			
22	772 ± 2.2	35.8 ± 0.4	12.1 ± 0.8	16.1 ± 1.1	111 ± 1.4	76.5 ± 0.7

TABLE 5.—*Average Distribution of Water, Expressed in Percentages of Fat-Free Weight; Concentration of Nitrogen, Potassium and Phosphorus Per Liter of Intracellular Water, and Content of "Excess" Sodium Per Kilogram of Fat-Free Tissue in Muscles of Control and of Experimental Animals*

Extracellular Water, Percentage	Intracellular Water, Percentage	Intracellular Nitrogen, Gm.	Intracellular Potassium, mEq.	Intracellular Phosphorus, mM	Potassium-Nitrogen Ratio	"Excess" Sodium, mEq.
			Group 1. Control Animals			
9.8 ± 0.31	67.8 ± 0.23	50.9 ± 0.4	157 ± 1.2	111 ± 0.8	3.10 ± 0.02	3.00 ± 0.10
			Group 2. Animals During Hypoglycemic State			
8.3 ± 0.32	69.0 ± 0.21	50.6 ± 0.5	154 ± 0.9	108 ± 0.9	3.07 ± 0.04	5.90 ± 0.25
			Groups 3 and 4. Animals Which Survived Severe Hypoglycemia			
9.4 ± 0.60	67.9 ± 0.4	52.8 ± 0.6	163 ± 1.9	113 ± 1.1	3.11 ± 0.05	1.80 ± 0.15

these experiments as a result of hypoglycemic convulsions) agrees with the findings of other investigators using electrical stimulation.[12] However, no loss of intracellular potassium could be demonstrated. It

12. Fenn, W. O.; Cobb, D. M.; Manery, J. F., and Bloor, W. R.: Electrolyte Changes in Cat Muscle During Stimulation, Am. J. Physiol. **121**:595, 1938. Tipton, S. R.: Electrolyte Changes in Cat Muscle During Activity, ibid. **123**:203, 1938.

should be emphasized that the changes in the muscle are probably too slight to be adequately demonstrated by this method of investigation. Certain trends, however, are suggestive.

COMMENT

The demonstration of a redistribution of water in the brain with cerebral cellular swelling during insulin hypoglycemia (group 2) has certain interesting implications. Because of the nature of the experimental procedure, confirmation of this shift of water into the cell in human subjects under similar conditions is not likely. However, the similarity in the clinical picture of hypoglycemia in human beings to that exhibited by the experimental animals suggests that similar physicochemical changes may be present.

The mechanism responsible for the shift of water into the cell during hypoglycemia is at present not clear. Extended discussion along this line will prove unprofitable as long as knowledge of the base-binding capacity of the cellular proteins and organic acids and the changes in the hydrogen ion concentration taking place in the brain during insulin hypoglycemia is so limited. It seems rational, however, for the time being to assume that the shift of water represents a response to changes in the osmotic pressure inside the cell, associated with disturbances in ionic dissociation. The primary cause of these changes must be left for future elucidation.

It is a tempting hypothesis to assume that there exists a causal relation between the shift of water into the cell and the neurologic phenomena, especially the convulsions, exhibited by the animals. The observations of Drabkin and Ravdin [2] on the inhibiting effect of dehydration on the convulsive phenomena after insulin, as well as those of McQuarrie [1b] and others, cited by Fay,[1a] on the relation of body hydration to epileptic convulsions lend some support to this assumption. It must be remembered, however, that probably more fundamental factors than the shift of water are involved. These factors, capable of influencing the internal osmotic pressure, in all probability play an important role in the physiologic manifestations which ensue. It should also be mentioned in this connection that procedures designed to cause a shift of water into the cells without changing the total quantity of body water—the shift, for example, which results from depletion of extracellular electrolytes—do not tend to produce convulsions.[13] Preliminary experiments in this laboratory have shown that under these conditions the brain cells participate in the redistribution of water.

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13. Darrow, D. C., and Yannet, H.: The Changes in the Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:266, 1935.

Under ordinary conditions, clinical recovery from severe insulin hypoglycemia is associated with the finding of a normal distribution of water in the brain (group 3). In certain of the animals, however, evidence of extensive cerebral damage manifests itself (group 4). This can be demonstrated clinically, chemically and histologically. As has already been pointed out, the clinical picture exhibited by these animals bears a striking resemblance to that of the decerebrate animal. The histologic picture [10] is that of widespread necrobiosis of the cerebral ganglion cells, including the basal ganglia and the upper part of the medulla. Since no animal exhibiting this clinical picture was kept alive longer than forty-eight hours, it is not known what the subsequent histologic picture would be. However, all the evidence available leads one to suppose that, fundamentally, the changes encountered represent a relatively early phase in the disintegration of nonviable cells, the ultimate destiny of which is complete disappearance. The demonstration of the marked shift of sodium and potassium across the brain cell membrane, indicating loss of selective permeability of the membrane, as well as the marked loss of cellular water, might support this supposition. Unfortunately, there are available no comparable data bearing on the nature of the chemical changes associated with death of tissue cells to permit adequate discussion of these changes.

The possible mechanisms which have been suggested as being responsible for the marked cerebral damage produced by insulin hypoglycemia will be examined experimentally and discussed more completely in another publication.[14] It will suffice at this time to say that such factors as anoxemia or circulatory collapse, leading to impairment of cerebral circulation, were found to play little, if any, role in the experimental production of the cerebral lesions demonstrated in group 4. Data will be presented [14] which suggest that the direct action of insulin on the brain cells under certain conditions may be the injurious factor responsible for the damage to the brain.

The absence of any significant changes in the distribution of water and potassium in muscle during the course of or following insulin hypoglycemia needs little comment. The substantial carbohydrate reserves, as well as the ability to metabolize foodstuffs other than carbohydrates, would make prolonged hypoglycemia potentially less injurious to muscle than to brain. Since muscle represents so large a proportion of body water, it seems probable that procedures designed to vary the hydration of the body may exert their influence on the

14. Yannet, H., and Iannucci, J. F.: Experimental Study of Pathogenesis of Cerebral Changes Following Prolonged Insulin Hypoglycemia, Arch. Neurol. & Psychiat., to be published.

convulsive phenomena of hypoglycemia primarily by changes in the distribution of water in the brain rather than by affecting the hydration of the body as a whole.

SUMMARY

The effect of large doses of insulin on the distribution of water and electrolytes in brain and muscle was investigated. The changes occurring in the brain may be summarized as follows:

1. During the period of hypoglycemia, water passed from the extracellular spaces into the cells, leading to dilution of the cellular constituents.

2. About 60 per cent of the animals given a large dose of insulin survived without additional therapy. About half of these animals showed no demonstrable evidence of involvement of the central nervous system. The brains of these animals exhibited a slight loss of cellular potassium but no redistribution of water.

3. About half of the animals that survived under these conditions showed evidence of widespread cerebral damage. The symptoms presented were those characteristic of decerebrate rigidity. In the brains of these animals there was a marked shift of cellular water to the extracellular space, leading to pronounced shrinking of the cell and enlargement of the extracellular compartment. Associated with this shift of water there occurred a proportionately greater loss of cellular potassium, leading to a decrease in the concentration of intracellular potassium. It is suggested that osmotic equilibrium is maintained under these conditions by a transfer of sodium across the cell membrane.

4. No appreciable change in the total water content of the brain could be demonstrated in any of the animals given insulin. No significant changes in the distribution of water or potassium in muscle during or after severe hypoglycemia could be demonstrated.

ESTROGENIC THERAPY OF INVOLUTIONAL MELANCHOLIA

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Standardized estrogenic preparations have been in use for the past ten years.[1] There is general agreement that these substances are effective in the treatment of disorders of the climacteric, which are evidenced by such symptoms as hot flashes, dizziness, vasomotor imbalance and headache. Gynecologists are agreed that the majority of patients suffering from these menopausal symptoms are relieved, but admit that a few patients benefit little from treatment and that there is no adequate explanation of this failure. There is less agreement among psychiatrists as to the beneficial results of estrogenic therapy for involutional melancholia. Some workers [2] have been enthusiastic in recommending such treatment, while others [3] have reported results which seem to indicate that therapy of this type is not effective in cases of this disorder.

During the early years in which estrogenic substances were given to patients with involutional melancholia, the dose reported seems now, in the light of more recent investigation,[4] to have been inadequate. Except for the work of Papanicolaou and his associates, I am unaware of any research to determine the adequate dose of estrogen in treatment of involutional melancholia. In recently reported work of other investigators no attempt was made to measure the physiologic activity of the

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From the service of Dr. C. Macfie Campbell, the Boston Psychopathic Hospital.

1. Reese, H. H.; Paskind, H. A., and Sevringhaus, E. L.: Year Book of Neurology, Psychiatry and Endocrinology for 1937, Chicago, The Year Book Publishers, Inc., 1938, p. 660.

2. Ault, C. C.; Hoctor, E. F., and Werner, A. A.: Theelin Therapy in Psychoses: Effect in Involutional Melancholia and as Adjuvant in Other Mental Diseases, J. A. M. A. **109**:1786-1788 (Nov. 27) 1937. Suckle, J. E.: Treatment of Involutional Melancholia by Estrogen, ibid. **109**:203-204 (July 17) 1937. Werner, A. A.; Johns, G. A.; Hoctor, E. F.; Ault, C. C.; Kohler, L. H., and Weis, M. W.: Involutional Melancholia: Probable Etiology and Treatment, ibid. **103**:13-16 (July 7) 1934.

3. Schube, P. G.; McManamy, M. C.; Frapp, C. E., and Houser, G. F.: Involutional Melancholia: Treatment with Theelin, Arch. Neurol. & Psychiat. **38**:505-512 (Sept.) 1937.

4. Papanicolaou, G. N., and Shorr, E.: Action of Ovarian Follicular Hormone in Menopause as Indicated by Vaginal Smears, Am. J. Obst. & Gynec. **31**:806-831 (May) 1936.

estrogen given, or even to determine whether it was potent. Investigators during the past two years have reported various methods of testing the activity of estrogenic substances. The most widely accepted method is the vaginal smear test. It has been well established [5] that the vaginal epithelium alters considerably during the life of a woman and responds in a specific manner to estrogenic therapy. In normal women who menstruate regularly the vaginal epithelium is typically of the flat pavement type, with clearly defined cells and small pyknotic nuclei, and there is little evidence of leukocytic infiltration or infection in the vaginal smear. The patient in menopause, who has inadequate production of estrogen, will present a different picture. There is marked evidence of leukocyte infiltration, usually accompanied by infection. The vaginal mucosa tends to be typically senile in appearance, with deeply staining, oval epithelial cells, having large nuclei and little cytoplasm, and there is no evidence of the pavement type of epithelium. If adequate estrogen is given these women a complete change is noted,[4] indicating a shift from the menopausal to the normal type of vaginal mucosa; this occurs only if an adequate dose of estrogen is given. Two other methods [6] of testing the potency of estrogenic substances and determining the adequacy of the dose have been used by gynecologists and serve to substantiate the findings in the vaginal smear. The acidity and alkalinity of the vaginal secretions are known to vary with the activity of estrogenic hormone. Normally, menstruating women have an acid secretion, while women after the menopause and girls before the onset of menstruation have either neutral or mildly alkaline vaginal secretion.[6a] It is also known that in women who menstruate regularly the vaginal mucosa stains a deep mahogany brown when compound solution of iodine is applied, while the vaginal mucosa of women in menopause takes the stain poorly or not at all. When adequate estrogen is supplied to these women the p_H of the secretion shifts from the alkaline to the acid side, and the stain with compound solution of iodine changes in the manner described.

In the present series of patients who presented a typical picture of involutional melancholia [7] these three tests—examination of the vaginal

5. Papanicolaou, G. N.: Sexual Cycle in the Human Female as Revealed by Vaginal Smears, Am. J. Anat. (supp.) **52**:519-637 (May) 1933. Papanicolaou and Shorr.[4]

6. (*a*) Lewis, R. M., and Weinstein, L.: Production of Vaginal Acidity by Estrin: Its Importance in the Treatment of Gonorrheal Vaginitis, Surg., Gynec. & Obst. **63**:640-643 (Nov.) 1936. (*b*) Krumm, J. F.: Variations in the Glycogen Content of Vaginal Mucosa as Relative Index to Quantitative Amount of Ovarian Hormone Available in Organism, Am. J. Obst. & Gynec. **31**:1035-1037 (June) 1936.

7. Henderson, D. K., and Gillespie, R. D.: A Textbook of Psychiatry for Students and Practitioners, ed. 2, New York, Oxford University Press, 1932.

smear, determination of the p_H of the vaginal secretion and observation of the staining response of the vaginal mucosa to compound solution of iodine—were utilized to determine the activity of the estrogen. Although these methods have been used individually in determining the potency of estrogenic substances employed in treating the physiologic symptoms of the menopause, I am unaware of any study in which a series of patients with involutional melancholia have been followed in this manner. No males were included in the series, as there is as yet no reliable method of determining hormonal activity in the male and no assurance that estrogen could be a substitute for androgen.

The problem of treating patients of this type is unusually complex; undoubtedly there are many factors other than endocrine deficiency which determine the course of the psychosis. Titley [8] went to considerable pains to describe the personality of patients with involutional melancholia, with their uniform and special pattern of reaction, which is firmly fixed before the psychosis develops. In addition, there are undoubtedly changes in other endocrine glands associated with the menopause (notably the pituitary and the thyroid, and possibly the adrenal gland) which may be irreversible after prolonged activity. Arteriosclerosis with hypertension and the resulting physiologic disorder may further complicate treatment of these patients. The important consideration in therapy is whether estrogen given in adequate doses will reduce or abolish the marked tension and agitation and restore the mental equilibrium of patients with a certain psychic makeup in whom a psychosis has been precipitated by the marked endocrine changes occurring at the climacteric.

REPORT OF CASES

The following histories of patients treated with estradiol benzoate (progynon B[8a]) are presented.

CASE 1.—*A married woman aged 50, of neat, orderly, worrisome, unsociable, religious personality, one and one-half years after the menopause produced by radium therapy presented mental symptoms of depression, agitation, somatic delusions and ideas of sinfulness. Physical symptoms were premature senility, general cachexia, hirsutism of the face, dry skin and scanty hair. Estradiol benzoate injected intramuscularly resulted in improvement after four weeks; this lasted for six weeks and was followed by relapse, with no improvement after further large doses of the estrogen. The vaginal smear indicated that the estrogen was active. The patient died of intercurrent disease.*

8. Titley, W. B.: Prepsychotic Personality of Patients with Involutional Melancholia, Arch. Neurol. & Psychiat. **36**:19-33 (July) 1936; Prepsychotic Personality of Patients with Agitated Depression, ibid. **39**:333-342 (Feb.) 1938.

8a. The Schering Corporation, Bloomfield, N. J., supplied the progynon B used in this investigation.

Clinical History.—An Irish housewife aged 50, with no history of mental disease in the family or previous psychotic episodes, was described as having been quiet and sensitive, with few friends or interests outside her home, unusually neat, orderly and economical, a good housekeeper and inclined to worry about trivial matters. She was religious. The menses had started at the age of 14. She married at 22 years and was sexually frigid. There were two pregnancies; one resulted in a miscarriage; one child died at the age of 8 months, of convulsions. The menses were regular and normal until the age of 48, when she had menorrhagia and metrorrhagia, due to uterine fibroids. Treatment with radium was followed by complete cessation of menses, hot flashes, dizziness, headache, sweating associated with agitation, depression, loss of interest in the home and ideas of sinfulness. She entered the hospital one and one-half years after cessation of the menses. Here she was unusually agitated, tearful and self accusatory; she slept and ate poorly, had many somatic delusions, such as having "no stomach, no head, no blood," said that she was dead and reiterated the phrases: "What have I done? No one likes me."

Physical Examination.—There was premature senility; the hair was coarse, scanty and gray, and the patient pulled it out in handfuls. The skin was dry; there was hirsutism of the face. No neurologic signs were found. Arteriosclerosis was definite, the blood pressure being 200 systolic and 130 diastolic. After treatment with estradiol benzoate it fell to 130 systolic and 90 diastolic; this was followed by a rise after treatment had been discontinued.

Course.—After two months in the hospital, estradiol benzoate was started and continued for twenty-two weeks; 30,000 international units was given intramuscularly each week. The patient became more agitated during the first four weeks of treatment; then for six weeks with the same dose she improved, showing less agitation and sleeping and eating better. The vaginal smear, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine showed slight evidence of activity of the estrogen. Proluton (a preparation of corpus luteum), in doses of 2 ampules each, injected intramuscularly, was therefore added to the estradiol benzoate to enhance the activity of the estrogen.[9] The following week the patient became violent, screaming and tearing at her hair, clothing and body. She later displayed rhythmic swaying movements, associated with repetitive screaming of certain phrases. Extreme motor restlessness lasted one week. Estrogenic therapy was discontinued for one week, then started at 50,000 international units (intramuscularly); within the next six weeks the dose was increased to 180,000 international units and was maintained at about 160,000 international units weekly for four weeks thereafter. The vaginal smear, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine showed complete response. The patient's mental symptoms did not improve. There were more hirsutism, loss of weight and evidence of cachexia than had previously been noted. Estrogenic therapy was discontinued at the end of twenty-two weeks, after a total of 1,300,000 international units of estradiol benzoate had been given. The patient remained in the hospital four months after treatment was discontinued. The vaginal smear, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine showed complete reversal to the menopausal type. The patient became even more agitated than while under treatment. There developed many cutaneous infections,

9. Smith, G. Van S.: Personal communication to the author.

parotitis, erysipelas of the face and bronchitis. She was transferred to another state hospital, where she died in a few weeks of pulmonary and cardiac disease. No autopsy was done.

CASE 2.—*A married woman, unsociable, meticulous, emotionally unstable, religious and sexually frigid, had had irregular, profuse, painful menses; panhysterectomy at 28 was followed immediately by headaches, dizziness, hot flashes, agitation, depression and suicidal thoughts. There were moderate obesity, scanty hair and dry skin. Administration of estradiol benzoate was followed by definite improvement, with reduction of agitation and depression.*

Clinical History.—A housewife aged 28, with no history of previous psychosis or of mental disorder in the family had been considered nervous, a poor mixer, unsociable, with narrow interests and limited ability to adapt to new situations, and religious. She was a good housekeeper and was neat and meticulous. Onset of the menses occurred at the age of 18; the periods were painful, irregular and profuse. She was sexually frigid. There was a history of three spontaneous miscarriages, followed by the birth of two living children, now aged 3 and 8 years, respectively. The patient had complained of pelvic pain for many years. The first pelvic operation was performed eight years before admission and was followed by three others, the last occurring ten months before admission, when the uterus and the remaining ovarian tissue were removed. About one month after the operation the patient became agitated, sleepless and depressed, had ideas of suicide and threatened to kill both her children and herself. She complained of dizziness, frequent hot flashes, headaches and hot and cold sweats.

Examination.—The patient was obese and had dry skin and scanty hair; there was evidence of panhysterectomy. Examinations of the blood and urine gave normal results. The cholesterol of the blood measured 340 mg. per hundred cubic centimeters; the basal metabolic rate was —8 per cent.

Mentally, there were marked agitation, weeping, changeability of mood, depression, ideas of suicide, feelings of remorse and self accusation, fear and apprehension of having cancer.

Course.—The patient had received 200,000 international units of estrogenic substance in the eight months before admission, but none recently. One week after admission estradiol benzoate was given intramuscularly in doses of 30,000 international units for the first week, and then in doses of 70,000 international units weekly for four weeks. Marked reduction in the patient's agitation and emotional instability was noted. Headaches, dizziness and hot flashes were lessened in severity. Vaginal smears, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine gave definite evidence that the estrogen was effective. These changes in the vaginal mucosa coincided with the clinical improvement.

CASE 3.—*A married woman, quiet, retiring, unsociable and meticulous, had had irregular menses for two years. Cessation of menstruation six months before the first admission was followed by hot flashes, increased tension, agitation, depression and suicidal attempts. Estrogen was given for three months; the menses were reestablished, and the mental symptoms disappeared. Five years later she was admitted a second time, with a history of regular menses for four years, followed by irregularity and, for six months, a return of agitation, depression and suicidal attempts. Estradiol benzoate was given for four weeks, with evidence in the*

vaginal smear, the p_H of vaginal secretions and the response of the vaginal mucosa to compound solution of iodine that the estrogen was effective. There was coincident reduction of agitation and depression.

Clinical History.—A Jewish housewife aged 42, with no history of mental disorder in the family and no previous psychosis, had been quiet and retiring, with few interests outside her home, and had not made friends easily. She was neat and meticulous about her home. She had had little sexual drive prior to the onset of her mental illness. The menses started at the age of 12 and were regular and normal. There had been no pregnancies. There was a history of scanty, irregular menses for two years. Six months prior to admission menstruation ceased; there were increased sexual desire, hot flashes accompanied by a feeling of tension, agitation and depression, episodes of weeping and threats and attempts to commit suicide. Mentally, the patient showed marked motor restlessness, sleeplessness and poor appetite, with feelings of guilt and depression. The physical and laboratory findings were normal. She was given follutein (a preparation containing the anterior pituitary-like gonadotropic hormone from the urine of pregnant women) and amniotin (an estrogenic preparation originally derived from amniotic fluid), in unknown amounts, for about three months. The menses were reestablished. The mental symptoms disappeared completely. The menstrual periods continued to be regular and normal for over four years.

About one year before the patient's second admission, which was five years after the first, the menses became irregular; they stopped six months before her second entry. She had hot flashes and some dizziness. Six weeks before entry she became restless, tense, depressed and sleepless, had poor appetite, took no interest in her home and fretted over trivial matters. She threatened and attempted suicide. She had three weeks of treatment with an estrogenic substance (amount unknown) before coming to the hospital.

Physical Examination.—At the second admission the results of examination were normal. The cholesterol of the blood measured 244 and 256 mg. on two determinations.

Course.—Estradiol benzoate was given intramuscularly in doses of 10,000 international units twice weekly for four weeks. The patient improved. The agitation, depression, hot flashes and dizziness disappeared. Vaginal smears, the p_H of vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine indicated that the estrogen was effective. The menses were not reestablished. The patient was allowed to return home, where her local physician maintained therapy with a weekly dose of from 10,000 to 20,000 international units of estradiol benzoate.

CASE 4.—*A woman, quiet, retiring, religious, conscientious and meticulous, had had spontaneous cessation of menses five years before, followed by hot flushes, dizziness and headache, which was more marked in the last year. There had been lack of energy for two years, with loss of 40 pounds (18.1 Kg.) in weight. For two months she had been agitated and depressed and had expressed ideas of sinfulness. She had attempted suicide. She was treated with large doses of estradiol benzoate. The vaginal smear, the p_H of the secretions and the stain of the vaginal mucosa with compound solution of iodine indicated the effectiveness of the estrogen, which was coincident with improvement in the mental symptoms.*

Clinical History.—A housewife aged 56, with no family history of mental disease, was described as a quiet, retiring person, who never took the initiative in making friends, was religious and had no outside activities except in her church.

She was a careful housekeeper and was neat and orderly in her personal habits and dress. She was extremely reluctant to speak of sexual topics. She fretted over trifling matters and worried over insignificant physical complaints. She tended to be stubborn and firmly fixed in her beliefs. Menses were established early and were regular and normal until five years before entry, when they gradually lessened, became irregular and stopped entirely. Since, she had had headaches, hot flashes, dizziness and tinnitus, which had been more marked in the last year. Vaginal discharge had recently become profuse. There had been lack of energy for the past two years, with loss of 40 pounds (18.1 Kg.) in weight.

The onset of mental symptoms occurred two months before entry, when the patient became agitated and depressed and expressed ideas of guilt in relation to her past sex life. Many somatic delusions were present. She made two attempts at suicide before entry.

In the hospital the patient showed marked motor restlessness, tension and agitation, with ideas of sinfulness, somatic delusions and the belief that other patients called her a "bad woman."

Physical Examination.—There were loss of weight, moderate arteriosclerosis and chronic otitis media on the left. The blood pressure on admission was 200 systolic and 120 diastolic. With treatment the pressure fell to 130 systolic and 76 diastolic. Examination of the blood and urine revealed nothing unusual. The cholesterol measured 182 mg.; the basal metabolic rate was + 17 per cent (the patient was extremely agitated).

Course.—Estradiol benzoate was given intramuscularly in doses of 150,000 international units weekly, in three doses. After 1,000,000 international units had been given the dose was decreased to 100,000 international units weekly, in two doses, then to 30,000 international units weekly for four weeks and, for the last three weeks in the hospital, to 50,000 international units per week. A total of 1,470,000 international units was given. Improvement was noted one week after treatment was started. Maximum improvement was noted after about five weeks of treatment. Vaginal smears, the p_H of vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine gave definite evidence that the estradiol benzoate was active. The vaginal discharge disappeared. Hot flashes and headaches were abolished. Menstrual bleeding occurred two months after treatment was started, but only once. The marked tension, agitation and depression disappeared. The patient returned home after three months in the hospital. She receives a maintenance dose of 20,000 international units of estradiol benzoate weekly.

CASE 5.—*A stubborn, complaining, meticulous, religious woman, inclined to worry, had had spontaneous cessation of menses fourteen months before entry, followed by headaches, hot flashes and dizziness, which increased in severity. The husband died one year before admission, and two months later she became depressed and agitated, lost interest in her home and child and threatened suicide. Estradiol benzoate, in large doses, brought about indication of its activity, coincident with definite improvement of mental symptoms.*

Clinical History.—An Irish housewife aged 47, with no history of mental disease in her family or past life, was described as worrisome, anxious and easily disturbed over trival matters. She was a good housekeeper and was neat and meticulous; she was religious and had few outside interests or close friends. She was stubborn and fixed in her habits. Menses were established early and were regular and normal. She had had two miscarriages, followed by a full term,

normal child, now 10 years of age. Two years before admission the menses became irregular, and fourteen months before admission they stopped entirely. One year before entry her husband died. About two months after his death she complained of headaches, hot flashes and dizziness. She became tense, agitated and depressed and threatened suicide. She lost interest in her home and child and expressed many somatic delusions, complaining that she felt unreal, that her blood was not circulating and that food would not digest.

Examination.—The findings were not unusual, except for a prematurely aged appearance, loss of weight, dry skin and coarse hair. The cholesterol of the blood measured 200 mg.; the basal metabolic rate was —5 per cent.

Mentally, the patient was extremely tense and agitated and displayed marked motor restlessness, many self-accusatory ideas and somatic delusions.

Course.—Estradiol benzoate, 150,000 international units, was given intramuscularly each week, in three doses. Improvement was observed in two weeks, as well as early changes in the vaginal smear, the p_H of vaginal secretions and the response of the vaginal mucosa to compound solution of iodine. The shift to the normal type was complete at about the fifth week of treatment. The patient's agitation and restlessness became less; she slept and ate better and was helpful about the ward. The blood pressure, which on entry was 140 systolic and 80 diastolic, fell to 120 systolic and 60 diastolic during treatment with estradiol benzoate. The first menstrual bleeding occurred six weeks after starting estradiol benzoate and recurred at intervals of three weeks. Hot flashes, headache and dizziness were definitely improved. The patient gained about 30 pounds (13.6 Kg.) in weight during four months. A total of 1,290,000 international units of estradiol benzoate was given while she was in the hospital, over a period of three months. She was sent home, with instructions to continue treatment with a maintenance dose of 20,000 international units of estradiol benzoate weekly, later to be reduced to 10,000 units.

CASE 6.—*A conscientious, religious, meticulous woman, whose menses had been irregular and scanty for three years, with associated headaches and dizziness, became agitated and depressed and threatened suicide. There were malnutrition and hypochromic anemia, with brownish pigmentation over the face and trunk; the chloride content of the blood was low; there was no evidence of tuberculosis; polyglandular dysfunction was evident. With estradiol benzoate the agitation lessened. There was diarrhea for two weeks, followed by vascular collapse in spite of intravenous administration of extract of adrenal cortex and a solution of sodium chloride. The patient died, presumably as the result of an adrenal crisis, of two days' duration. Autopsy revealed edema of the adrenal cortex, with hyperemia and decrease in fat; fibrosis of the ovaries, with increased vascularity and absence of follicles; a normal thyroid; an adenomatous arrangement in a small nodule of the pituitary, but no atrophy of the gland; no cerebral lesions.*

Clinical History.—A married housewife aged 48, with no history of mental disorder in the family, had had an episode of agitation and depression at the onset of her menses, when she was 13 years of age. At that time she was in a state hospital for mental disease for six months. The patient was unusually neat and meticulous in her personal habits and dress; she was conscientious and a hard worker. She had never wanted children, as she considered that they were "a nuisance and always cluttering up the house." She was religious and obtained most of

her recreation and pleasure from church activities. The menses were regular and normal until three years before admission, when she began to miss periods occasionally. In recent months she had had headaches and dizziness, but no hot flashes. About six weeks before admission she seemed to lose interest, became agitated and cried a great deal. She complained of past sins and thought the police were coming to punish her. She ate and slept poorly, threatened suicide and became extremely agitated.

Examination.—The patient was poorly nourished and asthenic, with a sallow, anemic appearance and scattered areas of brownish pigmentation over the face, trunk, abdomen and mucous membrane of the mouth. Roentgenograms of the chest and adrenal glands revealed no evidence of tuberculosis. Examination of the blood showed marked hypochromic anemia: hemoglobin, 8.5 mg. per cubic centimeter; red cells, 5,200,000; white cells, 21,600; differential count, normal; cholesterol, 222 mg. per hundred cubic centimeters; chlorides, 408 mg. The patient was too uncooperative to permit estimation of the basal metabolic rate.

Mentally the patient showed marked agitation and motor restlessness, self accusation and somatic delusions. She refused to eat and was fed by tube.

Course.—Estradiol benzoate, 150,000 international units weekly, was given intramuscularly in three doses of 50,000 units each. The patient was more agitated and resistive during the first four weeks of this treatment than before. She exposed herself, masturbated, was resistive and had to be fed by a tube. In view of the low chloride content of the blood, scattered areas of pigmentation and a blood pressure of 102 systolic and 72 diastolic, it was believed that adrenal dysfunction might form part of the endocrine picture. Sodium chloride, in doses of from 4 to 10 Gm. daily, was given in the tube feedings and intravenously, without any change in the physical findings or mental picture. The intense agitation and tension showed signs of lessening in the fourth week of estrogenic therapy. Vaginal smears, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine at this time indicated that the estradiol was active.

The patient died of vascular collapse and diarrhea of two days' duration, a reaction interpreted as primarily of adrenal origin. Extract of adrenal cortex and intravenous solution of sodium chloride were given, without success.

Autopsy.—The ovaries showed increased vascularity, absence of follicles and increased fibrosis. The adrenals were hyperemic and edematous and displayed definite loss of fat. The pituitary showed mild fibrosis and absence of atrophy, but there was an adenomatous arrangement of cells in a small nodule in the anterior lobe. The pancreas had undergone postmortem autolytic changes. The uterus showed a vascular mucosa, with recent hemorrhage. The thyroid was normal for the age of the patient. The bowel was edematous and pale, with no hemorrhages. Cells suggesting Endamoeba histolytica were observed, but there were no ingested red cells. No cerebral lesions were observed.

CASE 7.—*A woman, hard working, conscientious, meticulous and unsociable, in whom an artificial menopause was induced by panhysterectomy, had no symptoms other than fatigue and increased tension until eighteen months later, when she became worried, self accusatory, tense and agitated. There was marked asthenia. With estradiol benzoate in large doses the agitation lessened.*

Clinical History.—A spinster aged 50, with no history of mental disorder in her family and no previous psychosis, was considered a secretive, somewhat distant person, extremely conscientious and hard working. She had few recreational interests outside her place of employment, where she was said to have been

meticulous and precise. She was neat and tidy in dress and personal habits, tended to worry over trifles and had high ethical and moral standards. The menses started at the age of 14 and were regular but painful. Two years before entry the patient had undergone panhysterectomy, with removal of cystic ovaries. After this she presented no physiologic symptoms of the menopause except increased fatigue, nervousness and tension. Six months before admission she complained of being tired and of having no energy. She was given more responsibility at her place of employment and about five months before admission began to worry about her work. She ate poorly and slept little. She finally felt unable to carry on her work, became agitated and tense, cried a great deal and blamed herself for trivial or nonexisting difficulties. She felt she had no right to take a sickness benefit, that she was a thief and that she should be punished and sent to jail.

Examination.—The patient was asthenic and poorly nourished. Neurologic examination gave normal results. The blood pressure was 150 systolic and 80 diastolic (after treatment with estradiol benzoate this fell to 110 systolic and 60 diastolic). The mental picture during hospitalization was one of marked restlessness and agitation. The patient wore a distressed, apprehensive expression. She admitted being depressed and having thoughts of suicide. She had a feeling of guilt with regard to accepting sickness benefit. She fretted over trivial matters, wondered if she had made a mistake at work and was fearful that she would be sent to jail. Examination of the blood and urine gave normal results. The basal metabolic rate was —8 per cent.

Course.—The patient was given 150,000 international units of estradiol benzoate per week, in three doses of 50,000 units each for four weeks, and then 100,000 international units weekly, the dose being decreased to 50,000 units per week. There was marked reduction in the agitation and depression. Vaginal smears indicated that the estrogen was active. Moderate anxiety and depression persisted after eight weeks of treatment. At the time of writing, the patient has little insight into her illness and is considered improved, but not recovered.

COMMENT

Case 1 must be considered as one of therapeutic failure. However, even in this case there was considerable improvement during a month of treatment, only to be followed by recurrence of marked agitation, which persisted and increased after treatment was stopped. In this patient there was clinical evidence of irreversible changes in the endocrine glands (particularly the pituitary), with the development of what was considered pituitary cachexia, which, coupled with arteriosclerosis and hypertension, served to defeat any effort at estrogenic therapy.

Case 6 was also one of therapeutic failure. The patient showed lessening of agitation and tension after four weeks of treatment with estradiol benzoate. Here, again, there was evidence of irreversible endocrine dysfunction, the adrenal glands being primarily involved.

With increasing experience in the use of estrogen in the treatment of patients with involutional melancholia, it is believed advisable to start with large doses. According to the schedule of treatment finally decided on, each patient is given 150,000 international units of estradiol benzoate

per week, 50,000 units being injected intramuscularly three times a week. This dose should be continued for three or four weeks, depending on the changes in the vaginal smear, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine. These various indicators of estrogenic activity vary in each case, some showing a quicker and more complete response than others. If the vaginal mucosa shows changes indicating that the estrogen is effective, the dose is dropped to 100,000 international units, and then to 50,000 units, per week. Vaginal smears are taken at weekly intervals. An attempt is made to establish a maintenance dose of estrogen which not only will maintain the change in the vaginal mucosa but also will relieve the patient of the physiologic and mental symptoms of the disorder. Some patients may be maintained on as little as from 10,000 to 20,000 international units a week. Any form of therapy which will lessen the acute symptoms of this mental disorder and shorten the patient's stay in the hospital is worth the trial, as these patients not only are among the most difficult to care for, but when untreated show a prolonged course and a mortality rate far in excess of that of the general population and higher than that for any of the groups with functional psychoses, being almost twice that for the manic-depressive group and four times that for the dementia praecox group.[10] The most obvious reason for the high mortality rate appears to be the irreversible endocrine and physiologic changes which have occurred and make the patient more susceptible to intercurrent disease. These irreversible changes may also account for the failure of estrogenic therapy in certain cases in this series. The lessening of marked agitation and tension, so familiar in these patients, was believed to be correlated with evidence of activity of the estrogenic substance, as measured by the vaginal smear, the p_H of vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine.

No certain criteria, either mental or physical, which would give a clue to the responsiveness of the individual patient to estrogenic therapy were observed. It is believed, however, that every patient presenting definite evidence of involutional melancholia should be given an adequate therapeutic trial with estrogen.

SUMMARY AND CONCLUSION

Seven patients with the syndrome known as involutional melancholia were treated with large doses of estradiol benzoate, given intramuscularly. The effectiveness of this estrogen was tested at weekly intervals by examining vaginal smears, determining the p_H of the vaginal secre-

10. Malzberg, B.: Mortality Among Patients with Involutional Melancholia, Am. J. Psychiat. **93**:1231-1238 (March) 1937.

tions and observing the reaction of the vaginal mucosa to compound solution of iodine. The patient's improvement or failure to improve was correlated with the changes indicated by these three tests. Except in 2 cases (1 and 6) clinical improvement was definitely correlated with demonstrated effectiveness of the estrogen. The lessening and abolition of the acute agitation and tension were noted to occur from two to five weeks after the beginning of estrogenic therapy. The failure of this type of therapy in cases 1 and 6 was attributed to irreversible physiologic changes. An outline is given of the schedule of treatment with estrogen followed in this group of patients. No criteria, either physical or mental, foretell with certainty what benefit will result from estrogenic therapy. It is believed that every patient with involutional melancholia should be given a trial, an adequate dose of the estrogenic substance being used and its activity checked by observation of the changes in the vaginal smear, the p_H of the vaginal secretions and the stain of the vaginal mucosa with compound solution of iodine.

NOTE.—Since this paper was submitted, the patient in case 4 has returned to the hospital. Her improvement had been maintained until three weeks before readmission, when her local physician had discontinued estradiol benzoate. Her mental symptoms returned and were similar to those described on her first admission. Vaginal smears showed regression to the involutional type. Administration of estradiol benzoate, in doses of 150,000 international units weekly, again was accompanied by lessening of tension and agitation. Complete alleviation of the psychosis has not occurred, in spite of adequate hormonal therapy, and this serves to emphasize the complex character of this disorder.

LIPOIDS AND PROTEINS IN FLUID OBTAINED FROM APPROXIMATELY COMPLETE DRAINAGE OF THE CEREBROSPINAL SYSTEM

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There is considerable uncertainty with regard to the amounts, if any, of cholesterol and fatty acids in the spinal fluid, largely because the methods available are not sufficiently refined to measure accurately the small quantities in a few cubic centimeters of fluid. The large amounts (80 to 120 cc.) of cerebrospinal fluid removed in preparing patients for encephalographic examination have made it possible to obtain sufficient lipoid material for study. The proteins were determined by several methods in order to obtain data on the ratio between cholesterol and protein in spinal fluid. These results proved interesting in connection with previous studies on composition and formation of transudates.[1]

The early attempts of Mott [2] and of Mestrezat [3] to recover cholesterol from the cerebrospinal fluid of persons free from obvious meningeal disorders yielded nothing, or only very slight traces. Subsequent workers have reported finding amounts that ranged from zero to 14 mg. per hundred cubic centimeters. A review of the literature may be found in the chapter on lipoids in Katzenelbogen's monograph.[4] The most comprehensive recent study of these substances was reported by Plaut and others [5] in 1933 and 1935. These authors stated that the normal

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1. Man, E. B., and Peters, J. P.: Permeability of Capillaries to Plasma Lipoids, J. Clin. Investigation **12**:1031, 1933.

2. Mott, F. W.: The Oliver Sharpey Lectures on the Cerebrospinal Fluid, Lancet **2**:1 and 79, 1910.

3. Mestrezat, W.: Le liquide céphalo-rachidien normal et pathologique, valeur clinique de l'examen chimique, Paris, A. Maloine, 1912.

4. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1937, pp. 240-247.

5. Plaut, F., and Rudy, H.: Untersuchungen über den Cholesteringehalt des Liquor cerebrospinalis, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:229, 1933; Ueber die Beziehungen zwischen Blutcholesterin und Liquorcholesterin, ibid. **146**:262, 1933. Plaut, F., and Pruckner, F.: Zur Bestimmung des Cholesterins im Liquor cerebrospinalis, ibid. **154**:292, 1935.

values for cholesterol lay between 0.15 and 0.22 mg. per hundred cubic centimeters. In disagreement with these figures are the results summarized by Flexner,[6] who stated that no cholesterol could be found. The discrepancies between the findings of various investigators are probably due to differences in methods, the small amounts of cholesterol and, particularly, the generally recognized unreliability of colorimetric methods. The studies of Seuberling,[7] in 1938, on fatty acids and phosphatides appear to be the only ones reported in the literature. Normal values for fatty acids in lumbar fluid varied between 2 and 6 mg. per hundred cubic centimeters.

The spinal fluid contains sufficiently larger amounts of protein to make their determination comparatively easy and accurate. A number of methods have been employed, however, with variable reports as to the normal values. Mestrezat [8] used the roughly quantitative exploratory methods of drying and nephelometry and found amounts of protein ranging from 15 to 30 mg. per hundred cubic centimeters.

Hewitt [8] modified Wu's tungstic acid method for plasma proteins and measured the color produced by treatment of the precipitate with a phenol reagent. He reported an average normal value for proteins of 23 mg. per hundred cubic centimeters. Matz and Novick [9] introduced a further variation of the tungstic acid and phenol reagent principal and obtained values for 10 patients with nonmeningitic and nonsyphilitic diseases which ranged from 27 to 52 mg. per hundred cubic centimeters.

Kafka [10] investigated a number of methods for measuring spinal fluid proteins, including ammonium sulfate precipitation and the Kjeldahl and Esbach technics; on the basis of these extensive studies he stated that the average for total proteins was 24 mg. per hundred cubic centimeters, with the value for albumin 20 mg. and that for globulin 4 mg. per hundred cubic centimeters.

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6. Flexner, L. B.: Chemistry and Nature of the Cerebrospinal Fluid, Physiol. Rev. **14**:161, 1934.

7. Seuberling, O.: Ueber den Gehalt des Liquor cerebrospinalis an Fettsäuren, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:402, 1938.

8. Hewitt, L. F.: Proteins of the Cerebro-Spinal Fluid, Brit. J. Exper. Path. **8**:84, 1927.

9. Matz, P. B., and Novick, M.: Improved Colorimetric Procedures for the Quantitative Estimation of the Proteins of the Cerebro-Spinal Fluid, J. Lab. & Clin. Med. **15**:370, 1930.

10. Kafka, V.: Die Zerebrospinalflüssigkeit, Leipzig, Franz Deuticke, 1930.

The nephelometric method, devised by Denis, Ayer and Foster in 1920 and 1921 [11] and modified by Ayer, Dailey and Fremont-Smith [12] in 1931, is simple and sufficiently accurate for clinical purposes. It has been employed almost routinely in two Boston hospitals, and the results of these observations have been summarized in the monograph by Merritt and Fremont-Smith.[13] They concluded that the protein content of normal lumbar cerebrospinal fluid as measured by this method varies between 15 and 45 mg. per hundred cubic centimeters. Fluid from the cisterna magna and from the ventricles contains between 15 and 25 and 5 and 15 mg., respectively, per hundred cubic centimeters.

In the present study three methods of measuring spinal fluid proteins were compared. The method of digitonin precipitation was employed to measure cholesterol,[14] and the fatty acids were determined by saponification and titration.[15] In addition, the relations between these substances in the blood and those in the spinal fluid were investigated. The patients included in this paper were free from meningeal disorders and did not have syphilis. The encephalograms were made to rule out obscure intracranial pathologic conditions. In all but 4 subjects the cell counts on the fluid yielded less than 5 cells, and the other constituents can be considered as having approximately normal values.

These data should therefore yield evidence as to the probable normal amounts of cholesterol, fatty acids and proteins in the cerebrospinal fluid. With the relatively large volumes of material, the results should be sufficiently accurate to determine the relation between the quantities of lipoids and of proteins in spinal fluid and, in turn, to compare these amounts with those in serum.

METHODS

Methods of Obtaining the Fluid.—The spinal fluid used in these determinations was collected when the cerebrospinal system of each patient was drained and air injected for purposes of encephalographic examination. The patient was placed in a sitting position, and a lumbar puncture was done in the third or fourth lumbar

11. Denis, W., and Ayer, J. B.: A Method for the Quantitative Determination of Protein in Cerebrospinal Fluid, Arch. Int. Med. **26**:436 (Oct.) 1920. Ayer, J. B., and Foster, H. E.: Quantitative Estimation of the Total Protein in the Cerebrospinal Fluid, J. A. M. A. **77**:365 (July 30) 1921.

12. Ayer, J. B.; Dailey, M. E., and Fremont-Smith, F.: Denis-Ayer Method for the Quantitative Estimation of Protein in the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **26**:1038 (Nov.) 1931.

13. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1937.

14. Man, E. B., and Peters, J. P.: Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method with a Note on the Estimation of Lipoid Phosphorus, J. Biol. Chem. **101**:685, 1933.

15. Man, E. B., and Gildea, E. F.: A Modification of the Stoddard and Drury Titrimetric Method for the Determination of the Fatty Acids in Blood Serum, J. Biol. Chem. **99**:43, 1932.

space. A syringe was attached to the needle and the fluid allowed to flow out under its own pressure, pushing the plunger back. As each 10 cc. of fluid was removed the same amount of air was injected. The first 10 cc. of fluid was dropped from the syringe into test tubes, to be sent to the clinical laboratory for cell count and Wassermann determinations. All of the remainder was placed in a clean glass beaker and transferred to the biochemical laboratory immediately.

The spinal fluid was always centrifuged before analysis and only the supernatant fluid used. In all but 2 analyses, determinations were started within two hours of taking the fluid. In the exceptional instances (cases 3 and 4) the spinal fluid was kept eighteen hours in the ice box before the analyses were commenced.

Fatty Acids.—Whenever the quantity of spinal fluid was sufficient, duplicate aliquots of 40 cc. were used. In 13 cases the total quantity necessitated using smaller aliquots, which ranged from 17.5 to 35 cc. In every instance duplicate determinations were made.

On a hot plate, insulated with wire gauze, the spinal fluid was evaporated to about 2 cc. Oxidation was minimized by bubbling nitrogen through the liquid during the whole process of ebullition and evaporation. The use of nitrogen helped to control the foaming, which was copious during the early stages of evaporation. Immediately after the volume of the fluid was diminished to approximately 2 cc., 25 cc. of alcohol and ether (3 parts of redistilled alcohol and 1 part of redistilled ether) was added, and the fatty acids were determined by the same method as for the estimation of serum fatty acids, previously described by Man and Gildea.[15]

Cholesterol.—Cholesterol was determined by the digitonin gravimetric procedure for serum cholesterol according to the technic of Man and Peters. Since the method was first published, a further step has been added to insure that only cholesterol digitonide is included in the weight of the precipitate. The precipitate of cholesterol digitonide, after being washed to constant weight, is dissolved in boiling methyl alcohol, which is filtered through the funnel. Subsequent to three washings with boiling methyl alcohol, boiling water is poured through the funnel. Since cholesterol digitonide is soluble in boiling methyl alcohol, the loss of weight before and after this washing represents the actual weight of cholesterol digitonide. This additional step in the method has been described recently.[16] However, the quantity of cholesterol in 40 cc. of spinal fluid is so small that all of the alcoholic extract, in which the fatty acids have been titrated, was used. This extract sometimes contained minute shreads of filter paper from the filter paper Gooch crucibles. Therefore the alcoholic extract was filtered through fat-free filter paper and the paper adequately washed with alcohol before the addition of digitonin to the combined filtrate and washings.

Protein.—The spinal fluid proteins were determined by three methods only when the quantity of fluid was sufficient. Unfortunately, in frequent cases the quantity did not permit these comparisons of the protein content. Therefore a method was developed in which the same aliquot of spinal fluid was used for determination of fatty acids, cholesterol and total proteins. All the nitrogen in the residue was determined [17] after the extraction of the fatty acids with alcohol and ether. Since

16. Bogdanovitch, S. B., and Man, E. B.: Effects of Castration, Theelin, Testosterone, and Antuitrin-S on the Lipoids of Blood, Liver and Muscle of Guinea Pigs, J. Physiol. **122**:73, 1938.

17. Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration: IV. Malnutrition and the Serum Proteins, J. Clin. Investigation **8**:577, 1930.

urea and amino acids are soluble in alcohol, it was assumed that all the nonprotein nitrogen, except possibly traces of creatinine and uric acid, was washed from the protein residue when the lipoid extract was filtered through filter paper, which was subsequently washed with seven 5 cc. portions of a 3:1 mixture of alcohol and ether. The duplicate filter papers and protein residues from the extracting flasks were then transferred to Kjeldahl flasks, and the total nitrogen was finally estimated after collection of the ammonia in 0.02 normal hydrochloric acid. In this instance filter paper was also used in the Kjeldahl blanks.

The Denis-Ayer method of estimating protein by measuring in a colorimeter the cloudiness after precipitation of the protein by sulfosalicylic acid was used in strict accordance with directions already published by these authors.[18]

The third method consisted of determining the total nitrogen in an aliquot of spinal fluid and then correcting for the nonprotein nitrogen. The total serum protein was calculated by the formula: 6.25 times (total nitrogen minus nonprotein nitrogen). Each of the duplicate aliquots of spinal fluid was usually 20 cc., though only 10 cc. was used for specimens 10 and 13 and only 8 cc. for specimen 11. Since the nonprotein nitrogen is often twice the protein nitrogen, this method is subject to a large experimental error unless the nonprotein nitrogen is meticulously determined.

Nonprotein Nitrogen.—It was found difficult to precipitate the protein in spinal fluid so that a clear, protein-free extract could be obtained. Filtering, even through hardened filter paper, was apt to give a slight turbidity in the extract. The method finally adopted was to employ equal volumes of spinal fluid and 10 per cent solution of trichloroacetic acid. After centrifuging for usually more than, but at least, ten minutes, the clear supernatant extract was siphoned from the precipitated protein. Duplicate aliquots of this extract, each containing the equivalent of 5 cc. of spinal fluid, were then analyzed for nitrogen by a micro-Kjeldahl method. Since the nonprotein nitrogen content of spinal fluid is small, the use of as much spinal fluid as this is necessary to minimize the percentage error of this method. The extract was digested with sulfuric acid, copper sulfate, potassium sulfate and, whenever necessary, small quantities of hydrogen peroxide (30 per cent). The ammonia was then distilled into 0.02 normal hydrochloric acid and the excess acid titrated with 0.02 normal sodium hydroxide.[19] Blank determinations on the reagents were made each time that the nonprotein nitrogen of the spinal fluid was determined.

The cases listed in the accompanying table are arranged in two major groups, the second group being divided into two subgroups (A and B). Group 1 (cases 1 to 15) includes all instances in which the encephalograms showed evidence of an intracranial pathologic condition. Group 2 (cases 16 to 26) includes all cases in which the encephalograms failed to show any evidence of intracranial pathologic change. All encephalograms were satisfactory except in 1 case (16), in which the plates were not interpretable. Within group 2, subgroup A includes cases in which there was clinical evidence of an intracranial pathologic condition in spite of failure to demonstrate it by encephalograms, while subgroup

18. Ayer, Dailey and Fremont-Smith.[12] Merritt and Fremont-Smith.[13]

19. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932.

B includes cases in which there was neither clinical nor encephalographic evidence of an intracranial pathologic condition.

In figure 1 the amounts of cholesterol are plotted against those of proteins, expressed in milligrams per hundred cubic centimeters. The cholesterol content of serum and that of cerebrospinal fluid, expressed

Comparison of Lipoids and Proteins in the Spinal Fluid and Serum of Twenty-Six Patients Without Meningitic or Syphilitic Disease

	Spinal Fluid						
				Protein			
Patient	Titrated Fatty Acids, MEq.	Cholesterol, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	From Fatty Acid Residue, Mg. per 100 Cc.	6.25 Total Nitrogen Minus Nonprotein Nitrogen, Mg. per 100 Cc.	Denis-Ayer Method, Mg. per 100 Cc.	Serum Cholesterol, Mg. per 100 Cc.
Group 1. Patients with Encephalograms Indicative of Intracranial Pathologic Condition							
1	0.037	0.24	..	..	..	..	184
2	0.024	0.38	..	28	..	..	...
3	.....	.....	13	30	27	..	...
4	0.011	0.32	..	38	..	..	...
5	0.010	0.34	..	..	..	..	...
6	0.102	0.40	..	..	..	..	...
7	0.016	0.48	..	27	..	..	189
8	0.070	0.26	8	19	28	..	...
9	0.042	0.46	9	29	33	25	...
10	X *	0.45	10	..	37	..	...
11	0.197	0.50	20	..	..	..	213
12	0.092	0.72	24	52	50	39	207
13	X	0.30	13	33	33	..	...
14	0.057	0.36	12	28	..	19	...
15	0.08	0.44	15	32	..	31	198
Group 2. Patients with Normal Encephalograms							
A. Neurologic Findings Indicative of Intracranial Pathologic Condition							
16	.....	0.48	..	36	..	..	...
17	0.102	0.34	11	29	36	27	...
18	0.082	0.42	7	29	32	27	...
19	.....	0.05	10	19	18	13	167
20	0.018	0.39	..	28	..	..	...
B No Positive Neurologic Signs Elicited							
21	0.067	0.46	..	..	..	..	...
22	X	0.47	12	44	39	..	204
23	0.005	0.32	..	..	..	..	222
24	0.044	0.44	..	..	..	..	163
25	0.020	0.34	..	26	..	..	180
26	0.10	0.6	..	40	..	44	200

* X indicates amount was too low to titrate.

in milligrams per hundred cubic centimeters, are compared in figure 2. Brief summaries of the cases are placed at the end of the paper.

RESULTS

In presenting the clinical data in the table, only the average values have been included. The patients were divided according to encephalographic and neurologic findings.

Cholesterol.—Each set of the 26 duplicate determinations of cholesterol agreed within 0.1 mg. per hundred cubic centimeters of spinal fluid

(except in cases 7, 10, 18 and 22). The average values for these 26 duplicate determinations ranged from 0.05 to 0.72 mg. per hundred cubic centimeters of spinal fluid, but the amounts, exclusive of 1 low and 1 high value, ranged from 0.24 to 0.60 mg. per hundred cubic

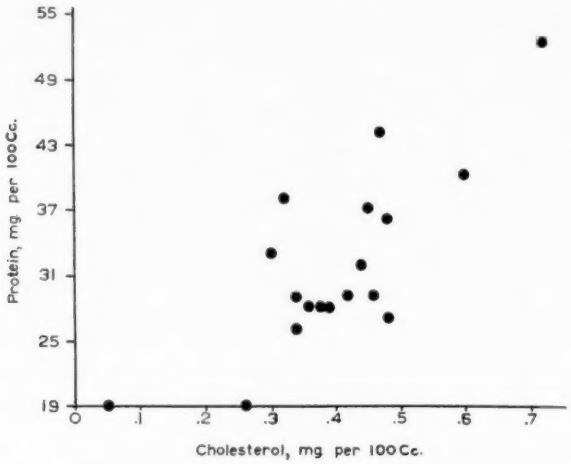

Fig. 1.—Chart showing relation of cholesterol to protein in the cerebrospinal fluid.

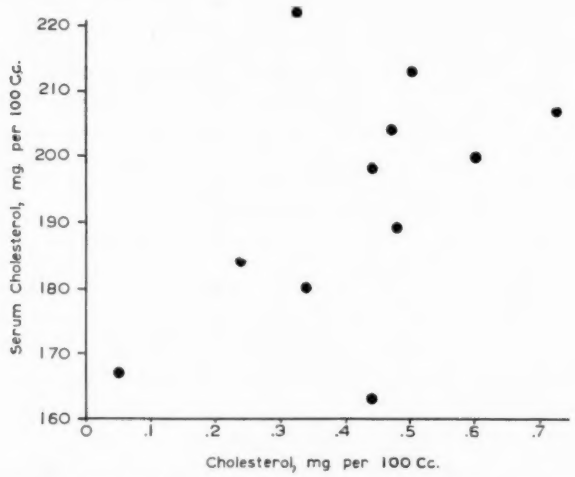

Fig. 2.—Chart showing relation of cholesterol in the serum to that in the cerebrospinal fluid.

centimeters. The average value for all the determinations was 0.39 mg. of cholesterol per hundred cubic centimeters of spinal fluid. This is higher than the values of 0.01 to 0.22 mg. of cholesterol per hundred cubic centimeters found by Plaut and Rudy.[5]

Fatty Acids.—The determined quantity of fatty acid is subject to considerable experimental error because the actual titer of fatty acids in 40 cc. of spinal fluid exceeds only slightly the blank reading for the method. On 24 patients determinations of fatty acids were made in which the results did not differ from those of duplicate determinations by more than 0.06 milliequivalent. The values ranged from untitrable amounts to 0.197 milliequivalent. Fourteen patients had fatty acids of 0.04 to 0.10 milliequivalent, or 1.1 to 2.69 mg. of tripalmitin per hundred cubic centimeters of spinal fluid. Two patients had fatty acids above this level, the highest value being 0.197 milliequivalent of fatty acids, and 8 patients had 0.02 milliequivalent or less.

Nonprotein Nitrogen.—Thirteen determinations of nonprotein nitrogen in the spinal fluid were made. The values ranged from 7 to 24 mg. per hundred cubic centimeters. These values correspond to those previously reported.[18]

In only 5 instances were all three determinations of protein made, although there were 9 comparisons of the two Kjeldahl methods. In these 9 cases the parallel values for total proteins agreed within 7 mg. or less per hundred cubic centimeters. Once the fatty acid residue gave the same results for the two Kjeldahl methods; four times the values for one Kjeldahl method were lower and four times higher than those for the other. Since the error for the nonprotein nitrogen method is 2 mg. per hundred cubic centimeters and since a difference of 2 mg. in nonprotein nitrogen will change the total protein content by 13 mg. per hundred cubic centimeters, this agreement seems as satisfactory as the methods permit. In 5 instances in which the three methods were compared the Denis-Ayer value was always the lowest. It differed from the lower value for the other two methods by 5, 2, 2, 11 and 4 mg., respectively, per hundred cubic centimeters and from the higher value for the other two methods by 6, 9, 8, 13 and 5 mg., respectively. While these differences are almost within the experimental errors, the fact that the Denis-Ayer method always gives lower results seems significant. The discrepancy between the values obtained by the Denis-Ayer method and those by the Kjeldahl determination on the fatty acid residue can hardly be attributed to the presence of uric acid and creatinine in the residue, for, according to Myers and Fine,[20] uric acid is almost completely absent from spinal fluid and the quantity of creatinine in 40 cc. of spinal fluid should be almost entirely soluble in the large amount of alcohol and ether used to extract the lipoids from the residue.

20. Myers, V. C., and Fine, M. S.: Comparative Distribution of Urea, Creatinine, Uric Acid and Sugar in the Blood and Spinal Fluid, J. Biol. Chem. **37:** 239, 1919.

It is noteworthy that, except in case 12, the values for proteins as measured by the Denis-Ayer method in the samples obtained by complete drainage were within the normal range, with an average of 30 mg. per hundred cubic centimeters. This is not far from the value of 28 mg. reported by Merritt and Fremont-Smith for lumbar fluid.[13] The fact that the cell counts varied from 0 to 5, with 4 exceptions in which there were a few red cells, indicates that other constituents of these fluids probably approximated normal values. The clinical studies (see "Report of Cases") also showed that most of the patients were suffering from slowly developing or nonprogressive disorders, probably not associated with any disturbance in the constituents of the cerebrospinal fluid. Patients 10 and 12 had active and progressive lesions, but patient 12 alone had unquestionably high values for proteins and cholesterol.

COMMENT

Measurable, but small, amounts of cholesterol were found in the cerebrospinal fluid of 26 patients. The range for all but 2 patients, who also had exceptional protein values, lay between 0.24 and 0.50 mg. This is considerably higher than the values of 0.06 to 0.22 mg. per hundred cubic centimeters reported by Plaut and Rudy[5] for essentially similar clinical material. The discrepancies in results can readily be explained by differences in methods. Plaut and Rudy had only 1 cc. aliquots of spinal fluid, and their method, which involved drying the cholesterol in a desiccator, is notorious for giving low results even when adequately large amounts of material are employed.

In view of the essentially normal results of encephalographic studies and the normal cell counts and nonprotein nitrogen and protein contents of the spinal fluid for the 11 patients of group 2, shown in the table, it is probable that the cholesterol values for these patients closely approximated those to be found in normal persons. It is also noteworthy that, with the exception of patient 12, the patients who showed no evidence of meningitis or syphilis and had normal proteins also had values for the cholesterol content of the spinal fluid within the range of those in group 2.

The fact that the amounts of fatty acids in the 40 cc. aliquots of spinal fluid barely exceeded the titer in the blank determinations introduces a large error in the quantitative results. It is clear, however, that fatty acids are present in spinal fluid and that they range from 1 to 3 mg. per hundred cubic centimeters. These values are lower than those of 6 mg. per hundred cubic centimeters reported by Seuberling,[7] but can be explained in part by dilution with ventricular fluid and in part by differences in method.

The protein values approximate those reported by Merritt and Fremont-Smith,[13] Kafka[10] and Hewitt.[8] A comparison of methods

revealed a fair agreement between the laborious titrimetric methods and the nephelometric method of Denis and Ayer.[12] It should be noted, however, that the latter, while accurate enough for clinical purposes, tends to give lower values.

That a close relationship exists between the amount of protein and the amount of cholesterol in spinal fluid is indicated by figure 1, in which the protein, expressed in milligrams per hundred cubic centimeters, is plotted against cholesterol, measured in milligrams per hundred cubic centimeters. The points fall roughly along a straight line, and their distribution is strikingly similar to that found for transudates by Man and Peters.[1] The fact that the concentrations were one-hundredth those of the transudates lends added significance to the observation that proteins and cholesterol tend to pass through relatively impermeable membranes in proportional amounts. The means by which this relation is maintained is uncertain, but could be explained by a loose linkage between proteins and cholesterol.

As in the case of the transudates, the fatty acids of the spinal fluid did not bear the close relation to the proteins that was observed for cholesterol. This cholesterol-protein relationship thus constitutes an additional point of similarity between transudates and spinal fluid. This may prove to be a further step toward the understanding of the formation of spinal fluid.

As suggested by Katzenelbogen,[4] the cholesterol-protein relation may depend on the state of the tissues (blood–cerebrospinal fluid barrier), which controls the formation of spinal fluid and may eventually prove useful as a test of their functional state.

Although previous authors, notably Plaut and Rudy,[5] have failed to discover any relation between cholesterol levels in the serum and those in the spinal fluid, the data presented in figure 2 suggest that such a relationship may exist under relatively normal conditions. A further study of this problem with large quantities of fluid in various pathologic conditions is therefore indicated.

CONCLUSIONS

Measurable amounts of cholesterol, ranging between 0.24 and 0.50 mg. per hundred cubic centimeters, were found in the cerebrospinal fluid of 26 patients who did not have meningitic or syphilitic disorders.

Fatty acids, calculated as tripalmitin, were also found, but in amounts of 1 to 3 mg. per hundred cubic centimeters, which were less than those previously reported by Seuberling.

A comparison of the results of two Kjeldahl methods for determining total proteins with those of the simple nephelometric method of Denis and Ayer showed agreement within 12 mg. per hundred cubic

centimeters, thereby confirming the reliability of the latter method for clinical investigations.

The amounts of protein and those of cholesterol in the cerebrospinal fluid varied directly and proportionally and in a manner similar to that previously observed in transudates.

Some of the theoretic and practical implications of these findings are discussed.

REPORT OF CASES

Group 1.—Case 1.—A well nourished housewife 36 years old complained of chronic headaches and weakness. There were irregular and sluggish pupils, slight paresis of the right side of the soft palate and hyperreflexia and absence of abdominal reflexes on the right side. An encephalogram showed enlarged sulci, suggesting atrophic areas. The diagnosis was a nonprogressive intracranial lesion complicated by hysterical behavior.

Case 2.—A well nourished woman 48 years old complained of chronic alcoholism and headaches. A bruit was heard over the suboccipital region and was louder on the left than on the right. Neurologic examination gave otherwise normal results. An encephalogram showed dilatation of the ventricular system. The diagnosis was intracranial aneurysm and psychopathic personality.

Case 3.—A man 40 years old complained of convulsive seizures. Neurologic examination gave normal results. An encephalogram showed dilatation of the ventricular system. The diagnosis was chronic convulsive state, of unknown origin.

Case 4.—A man 59 years old presented as the chief symptoms memory defect, hallucinations and disorientation. No positive neurologic signs were elicited. An encephalogram showed dilatation of the ventricles and cortical atrophy. The diagnosis was chronic alcoholism with deterioration and encephalopathy.

Case 5.—A boy 13 years old complained of convulsive seizures and retarded progress in school. He showed hydrocephalic formation of the skull, but no positive neurologic signs. An encephalogram showed hydrocephalus and porencephalic cysts. The diagnosis was hydrocephalus and porencephaly.

Case 6.—A man 44 years old complained of "peculiar spells." No positive neurologic signs were elicited. An encephalogram showed dilatation of the left lateral ventricle, dilatation of the sulci over the left cerebral hemisphere and cortical atrophy of the left cerebral hemisphere. The diagnosis was in agreement with the encephalographic findings.

Case 7.—A retired army officer 45 years old gave an eight year history of progressive retardation in mental capacity, weakness and malnutrition, following trauma to the head. The reflexes were all hyperactive, and there was generalized muscular weakness. An encephalogram showed increased convolutional markings. The diagnosis was intellectual and physical deterioration following trauma to the brain.

Case 8.—A woman 35 years old complained of having "fainting spells." No positive neurologic signs were elicited. An encephalogram showed cortical atrophy. The diagnosis was chronic convulsive state.

CASE 9.—A man 24 years old complained of headache, dizziness and ready fatigability following trauma. There were twitchings of the right nostril and eyelids and moderately hyperactive reflexes. An encephalogram showed widened cortical sulci. The diagnosis was post-traumatic changes, with vasomotor disturbances.

CASE 10.—A man 41 years old had a history of slowly developing Huntington's chorea. An encephalogram showed dilatation of the lateral ventricles, third ventricle and right temporal horn, The diagnosis was Huntington's chorea.

CASE 11.—A man 20 years old showed evidence of polyglandular disturbance. He complained of increasingly frequent spontaneous outbursts of temper followed by amnesia. No positive neurologic findings were elicited. An encephalogram showed dilatation of the lateral ventricles and of the third ventricle. The diagnosis was Fröhlich's syndrome and psychopathic personality presenting hysterical features.

CASE 12.—A man 56 years old complained of loss of ability to concentrate and loss of memory. There were poor muscular coordination, marked hyperkinesis and stuttering. An encephalogram showed dilatation of the lateral and third ventricles and calcification of gyri. The diagnosis was symptomatic psychosis with cerebral calcification.

CASE 13.—A man 30 years old complained of convulsive seizures and left occipital headaches. No positive neurologic signs were elicited. An encephalogram showed dilatation of the lateral ventricles, dilatation of cerebral sulci and cortical atrophy. The diagnosis was chronic convulsive state.

CASE 14.—A man 21 years old complained of convulsive seizures. No positive neurologic findings were elicited. An encephalogram showed widening of the cortical sulci and generalized cortical atrophy. The diganosis was chronic convulsive state.

CASE 15.—A man 55 years old for eight years had shown progressively increasing sensorial and intellectual deterioration. Neurologic findings were confined to impairment in orientation and recent memory and other intellectual functions. An encephalogram revealed extensive evidence of bilateral atrophy of the frontal cortex. The diagnosis was cerebral atrophy, of undetermined type.

Group 2 A.—CASE 16.—A boy 13 years of age manifested constant restlessness and incorrigibility. He had dysdiadokokinesis, more marked on the left than on the right; a peculiar shuffling gait, and choreic movements of the digits of the hands and feet when concentrating on being still. An encephalogram was not interpretable because of unsatisfactory filling of both the subarachnoid and the ventricular spaces. The diagnosis was organic drivenness.

CASE 17.—A man 31 years old had been stealing small articles for which he had no use. There was a history of considerable change in personality following a fracture of the skull. Neurologic examination gave normal results. An encephalogram was indeterminate. The diagnosis was intellectual deterioration following trauma to the brain.

CASE 18.—A well nourished woman 25 years old had a history of confusion and disorientation following an injury to the head, together with a series of epileptiform seizures. Neurologic examination gave normal results. An encephalogram was indeterminate. The diagnosis was post-traumatic syndrome with convulsions.

CASE 19.—A boy 15 years old gave a history of a series of peculiar "fits" and constant restlessness. Neurologic examination gave normal results. An encephalogram was indeterminate. The diagnosis was convulsive state, of unknown origin.

CASE 20.—A girl 13 years old had had a series of convulsive seizures. Neurologic examination gave normal results. An encephalogram was indeterminate. The diagnosis was convulsions, of unknown origin.

Group 2 B.—CASE 21.—A married woman 31 years old gave a history of gradual change in personality and inability to work. No clinical evidence of an intracranial pathologic condition was found. An encephalogram was indeterminate. The diagnosis was psychopathic personality, of anxious type.

CASE 22.—A man 38 years old made numerous physical complaints, with no clinical evidence of an intracranial pathologic condition. An encephalogram was indeterminate. The diagnosis was psychopathic personality, of hysterical type.

CASE 23.—A well nourished man 27 years old had shown loss of energy and depression in mood after an injury to the head. No clinical evidence of an intracranial pathologic lesion was discovered. An encephalogram was indeterminate. The diagnosis was manic-depressive depression.

CASE 24.—A feebleminded girl 12 years old showed evidence of polyglandular disturbances. No clinical evidence of an intracranial pathologic condition was detected. An encephalogram was indeterminate. The diagnosis was mental deficiency.

CASE 25.—A white man 24 years old had shown increasingly peculiar behavior and disorders of thinking. No clinical evidence of an intracranial pathologic condition was discovered. An encephalogram was indeterminate. The diagnosis was schizophrenia.

CASE 26.—A woman 38 years old complained of occasional convulsive seizures, beginning three years previously. No positive neurologic signs were elicited. An encephalogram was within normal limits. The diagnosis was convulsive seizures, of unknown origin.

Case Reports

SYPHILITIC POLYNEURITIS

A Clinicopathologic Entity

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In spite of the great frequency of syphilis of the central nervous system, it is rare that the peripheral nerves are involved. In fact, it is actually doubted by many that such a clinicopathologic entity as syphilitic neuritis exists. There are several reasons for this skepticism. Polyneuritis, as a neurologic symptom, is rather frequent generally, and there is no reason why nonsyphilitic multiple neuritis may not occur in a syphilitic person. Moreover, there are no clinical signs or symptoms which can specifically differentiate polyneuritis of syphilitic from that of nonsyphilitic origin, and this makes accurate diagnosis difficult. Most syphilitic patients are treated with bismuth, mercury and arsenical preparations; while neuritis as a result of therapeutic doses of these drugs is unusual it may occur, and the polyneuritis is often attributed to them. Though there are numerous clinical reports of syphilitic neuritis in the literature, detailed pathologic examinations have been strikingly few. It is remarkable that the condition is not observed more often, as syphilis is so common and involvement of the nervous system is certainly not infrequent. Nonne [1] indicated, however, that in recent years, since the introduction of arsenical therapy, there had been an increase in the frequency of this condition. Before the era of accurate serologic diagnosis, the disease may well have been attributed to infections or toxins, such as alcohol, since it was difficult to make a definite diagnosis in the late stages without an adequate clinical history. Although the possibility of syphilitic neuritis in the early stages of syphilis was accepted by some investigators, doubt of its presence in the so-called tertiary period has been expressed by most writers (Steinert,[2] Petrén [3]). The supposition that it may occur in the secondary and not in the tertiary period has been expressed by most writers (Steinert,[2] Petrén [3]). The the two.

Modern syphilology no longer adheres to the older chronologic classification of the clinical manifestations of syphilis into primary,

From St. Elizabeths Hospital, Washington, D. C.

1. Nonne, M.: Syphilis und Nervensystem, Berlin, S. Karger, 1924.

2. Steinert, H.: Ueber Polyneuritis syphilitica, München. med. Wchnschr. **56**: 1938, 1909.

3. Petrén, K.: Sur la question de la polynévrite syphilitique ou mercurielle: Observation d'un cas mortel, Nouv. iconog. de la Salpêtrière **28**:226, 1917.

secondary and tertiary periods. The fundamental pathologic reaction is the same in all stages. As Stokes [4] aptly pointed out:

> Relapse, recurrence and latency, which form comparatively small part of the calculations of the older chronological syphilology, are among the most essential features of the new and are quite outside the iron-clad succession of primary, secondary, and tertiary events that marked the thinking of all but the most observing minds of the last century.

In all stages of the disease the type of lesion is similar to that in the primary chancre, although many of the later reactions may be modified by allergic phenomena. The symptoms which follow depend on the localization of the process, especially when there is vascular involvement. Once the body has been penetrated by Spirochaeta pallida there is invasion of the vasa vasorum and perivascular lymphatics. This is followed by a reaction which expresses itself as a perivascular infiltration with lymphocytes and plasma cells, which may result in endothelial swelling and proliferation, leading to obliterative endarteritis, or in rupture of the wall of the vessel. During this phase the spirochetes increase rapidly in number and escape into the blood stream. However, even though a local lesion may apparently heal, the organisms may remain quiescent until tissue immunity decreases, when the organisms again reproduce, to be followed by reinoculation of the blood stream. Relapse, therefore, is distinctive of syphilis in all its stages, and the vascular changes are essentially similar in whatever stage they occur. With this conception of syphilis, it is unlikely that syphilitic neuritis could be confined to any one "stage" of the disease.

There is one strong clinical argument which speaks for the probability of syphilitic neuritis as a clinical entity; that is the therapeutic test. However, though there are many reports in the literature of cases of neuritis in which reaction to antisyphilitic therapy has been favorable, the existence of syphilitic neuritis is still open to doubt (Grinker,[5] Dana [6]).

In recent years there have been detailed reports with pathologic observations of only 2 cases of syphilitic neuritis (Margulis,[7] Popow [8]).

> The case described by Margulis [7] was that of a man aged 48 who was admitted to the hospital on March 14, 1929, complaining of pain in the back and lack of sensation in his lower extremities. There was a history of a primary lesion in 1920. He had received thirty injections of mercury and three of neoarsphenamine in 1920, but until 1928 had had no further treatment. In 1928 he had an alcoholic

4. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926.

5. Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934, p. 768.

6. Dana, C. L.: Nervous Diseases, ed. 10, New York, William Wood & Company, 1925, p. 267.

7. Margulis, M. S.: Ueber syphilitische Polyneuritis, Deutsche Ztschr. f. Nervenh. **115**:46, 1930.

8. Popow, N. A.: Ueber die syphilitische Polyneuritis, Deutsche Ztschr. f. Nervenh. **138**:217, 1935.

psychosis, and the Wassermann reaction of the blood was positive; four more injections of neoarsphenamine were given. Examination revealed paralysis of the lower extremities; paresis of the upper extremities; loss of tendon reflexes; hyperesthesia to pain; palpable, spindle-shaped thickening of the peripheral nerves; decrease in all forms of sensation at the distal portions of the extremities; severe pain and tenderness on pressure over nerves and muscles; atrophy of the small muscles of the hand and forearm, and atrophy of all muscles of the lower extremities. The Wassermann reactions of the blood and spinal fluid were positive. Increasing myocardial weakness developed, and the patient died one month after admission.

The postmortem observations were: vascular inflammatory changes in almost all organs and in the peripheral nerves; gummatous periendoneuritis with gummatous infiltration about the blood vessels of the perendoneurium, similar to miliary gummas. There was panarteritis, with fibrosis of the wall, intimal proliferation and sometimes complete obliteration of the lumen. Nerve fibers were decreased in number and were atrophic. The myelin sheaths and axis-cylinders were degenerated in an irregular fashion. The vessels of the brain, spinal cord, extremities, muscles and viscera showed changes similar to those in the nerves. Spirochetes were not demonstrated.

The case reported by Popow [8] was similar. The patient, a white man aged 58, was admitted to the hospital on Aug. 23, 1928, syphilis having been detected one year and a half previously. On admission he complained of pain in the left leg and fatigue on walking. The weakness gradually progressed until there were paralysis of the left foot and weakness of the right foot. The right patellar reflex was greater than the left, and both achilles reflexes were lost. There was hyperesthesia of the soles of the feet. The muscles and nerves were tender on pressure. The symptoms gradually decreased, and the patient was discharged. He was readmitted about six months later with paralysis of the left leg and weakness of the right leg, atrophy of muscles in the lower extremities, loss of the achilles reflexes, diminution in sensation of the distal portion of the left lower extremity and hyperesthesia on the right. Serologic tests of the blood and spinal fluid gave negative results. The patient died on April 8, 1929. Postmortem examination revealed general arteriosclerosis and myocarditis. The spinal roots and meninges showed no changes. The vasa of the peroneal, tibial and sciatic nerves showed perivascular infiltration, proliferation of the intima and obliterative endarteritis, with varying degrees of myelin degeneration. Spirochetes were not demonstrated. Popow diagnosed the condition as gummatous perineuritis.

REPORT OF A CASE

A. P., a white man aged 40, who was first admitted to the hospital on Dec. 28, 1933, had worked in his early years as a blacksmith. From 1916 until his hospitalization he had been a wrestler. He denied having had a primary syphilitic lesion. A positive Wassermann reaction of the blood was first discovered in November 1932. During one year prior to hospitalization he had received about forty intramuscular and about fifteen intravenous injections, the exact nature of which was not ascertained. There was no history of alcoholism or dietary restriction to indicate a possible vitamin deficiency.

In July 1933 there suddenly developed an attack of bilateral acute parotitis, which was accompanied by a skin eruption on the lower extremities. Since then, when walking, he felt as if he were "on a soft carpet." Occasionally he had lightning-like pains in the arches of his feet, severe enough to wake him at night.

His feet began to swell, and the pain became more intense. He sought hospitalization in a local institution on December 20, five months after the onset of his symptoms, and the next day was transferred to the psychopathic department of that hospital. Examination of the spinal fluid showed a 4 plus Kahn reaction, 160 mg. of protein per hundred cubic centimeters and a colloidal gold curve of 3333310000. It was said there were signs indicating intellectual deterioration, and he was described as having grandiose delusions. He was transferred to St. Elizabeths Hospital, pending investigation of his mental condition.

On admission he was quiet, cooperative and pleasant in manner. After admission he made a good behavior adjustment. Speech was clear, coherent and relevant, and there was no evidence of slurring. There was neither emotional disharmony nor euphoria. No hallucinations were elicited. Grandiose delusions were not in evidence. The psychologist reported his mental age as 11 years with the Stanford-Binet test, and it was noted that his intellectual impairment was in marked contrast to the good preservation of personality. Physical examination revealed nothing remarkable, except for the neurologic findings.

Neurologic Examination (Jan. 18, 1934).—The patient complained of numbness in both feet and of sharp, lightning-like pains in both insteps. The gait was a little unsteady and approached the so-called steppage type. He felt insecure on his feet, although there was no swaying in the Romberg position. There was no disturbance in function of the cranial nerves. The fundi showed no abnormality. The pupillary reactions were normal. A speech defect was not in evidence. No areas of disturbed sensibility were found on the trunk. The abdominal reflexes were not elicited. The cremasteric reflexes were weak on the right and absent on the left. The upper extremities showed no disturbance in motor, sensory or reflex function.

There were varicose veins and brownish pigmented areas on the skin of both legs. The right sciatic nerve was intensely tender to pressure. The Lasègue sign was negative on the left and strongly positive on the right. The patellar and suprapatellar reflexes were active and equal on the two sides. The achilles reflex was not elicited on either side. Signs of the Babinski group were not found. There was greatly diminished perception for light touch over the entire right foot. On the left, the toes alone showed diminished touch perception. Pain perception was increased on the sole of the right foot, and was normal on the sole of the left. Temperature perception was more impaired on the right than on the left. Sense of vibration was diminished over the right foot and was normal over the left. Sense of position and movement was lost in the toes of the right foot and was normal in those of the left. The achilles tendons were abnormally tender to pressure, more on the right than on the left. The serologic reactions were as follows: On Jan. 2, 1934, the Kolmer reaction of the blood was doubtfully positive; the Kahn reaction of the blood was positive. On January 3 the Kolmer reaction of the spinal fluid was strongly positive; the reaction for protein was 3 plus; there were 8 cells per cubic millimeter, and the colloidal gold curve was 1112221000.

Course.—On January 29, about one month after admission, the patient was discharged by court as being of sound mind, although there had been no essential change in his condition during his residence at the hospital.

The shooting pains in the legs and feet continued, with increasing severity. He consulted a local physician, who gave him two intravenous injections of neoarsphenamine and three intramuscular injections of a bismuth preparation. About March 1, 1934, he began to complain of weakness and numbness of the

right hand and of the three lateral fingers of the left hand and of weakness and numbness of both feet. He was readmitted to the psychopathic department of the city hospital on March 5, 1934. Examination of the spinal fluid showed a positive Kahn reaction, 150 mg. of globulin per hundred cubic centimeters and a colloidal gold curve of 5553320000.

Second Admission.—He was readmitted to St. Elizabeths Hospital on March 16, 1934, the weakness having progressed so far that he was brought to the hospital on a stretcher. He had lost considerable weight in the previous six weeks. He complained of numbness and weakness of the right hand; numbness and weakness of the first, second and third fingers of the left hand; numbness, tingling and paralysis of the right foot; weakness and intense pain in the left foot, and inability to walk or stand. Mental examination revealed essentially the same condition as on his previous admission. Physically, however, there was marked progression of neurologic signs.

Neurologic Examination (March 6): The pupils were equal and regular and reacted well to light and in accommodation. The fundi were normal. The cranial nerves showed no abnormality. The abdominal and cremasteric reflexes were absent. No sensory or motor disorder was present on the anterior or posterior aspect of the chest and abdomen. The right upper extremity showed no abnormality in tonus or coordination. There was no tenderness on pressure over the peripheral nerves and no vasomotor or trophic disorder. There was atrophy of the right hypothenar eminence, and the hand grip was weak. No objective sensory disorders were noted, however. The deep reflexes were all active. The left upper extremity showed no deformity or disorder of tonus or motion except for decreased motor power of the thumb and index and middle fingers. There was some atrophy of the thenar and hypothenar eminences. There was anesthesia for touch, pain, temperature and vibration over the left thumb, index finger and volar surface of the middle finger.

The muscles of the right leg were hypotonic, with foot drop. The right patellar and suprapatellar reflexes were active, but the achilles reflex was lost. The Babinski group of signs was not present. There were complete anesthesia for touch, pain, temperature and vibration and loss of sense of position and movement of the entire right foot and of almost the lower two thirds of the leg. The right achilles tendon was very tender to pressure. On the left, while there was no foot drop, there was definite weakness in movements of the toes and foot. Patellar and suprapatellar reflexes were active, but the achilles reflex could not be elicited. Anesthesia for all forms of sensation was present over an area similar to that on the right. There was extreme hypersensitivity on stroking either sole, and this caused an attack of severe, lancinating pain in the extremity.

Laboratory Examination: The hemoglobin content was 80 per cent; the white blood cell count varied between 14,500 and 17,000 per cubic millimeter, the differential count being 72 polymorphonuclears, 26 lymprocytes and 2 monocytes.

The Kolmer reaction of the blood was doubtfully positive; the Kahn reaction of the blood was positive. The Kolmer reaction of the spinal fluid was positive; the reaction for protein was 2 plus; there were 5 cells per cubic millimeter, and the colloidal gold curve was 2222211100.

Studies of the blood chemistry revealed 37.5 mg. of nonprotein nitrogen; 80.6 mg. of sugar; 8.7 mg. of calcium, and 3.38 mg. of phosphorus.

The basal metabolic rate was plus 40 per cent. This did not harmonize with the observation of the pulse rate, nor were other signs of hyperthyroidism present.

Twenty-four specimens of urine were examined for arsenic and bismuth. Examinations gave negative results for both.

Subsequent Course.—The patient remained bedridden throughout his stay in the hospital. Suddenly, on the morning of May 3, he lapsed into coma. Immediate examination revealed that respiration was slow, deep and stertorous. The blood pressure, which formerly was 140 systolic and 85 diastolic, was elevated to 260 systolic and 130 diastolic. The pupils were dilated and fixed. Examination of the eyegrounds showed marked choking of both disks. The spinal fluid was clear, the pressure being 15 mm. of mercury, and with pressure over the jugular veins, 26 mm. of mercury. Examination of the blood sugar showed a value of 200 mg. per hundred cubic centimeters. The patient died four hours later.

General Gross Postmortem Examination.—There were emaciation; old fracture of the seventh and eighth costal cartilages; scoliosis of the upper thoracic vertebrae; adhesions of the omentum; hypertrophy and infarction of the heart; mild atheromatosis of the aorta; old adhesions of the pleura; congestion and edema of the lungs; purulent bronchitis; cirrhosis of the liver; hydronephrosis; bilateral double ureters; hydroureter; acute splenic tumor; adenoma of the thyroid, and massive cerebral hemorrhage. The cause of death was given as cerebral hemorrhage.

Gross Examination of the Nervous System.—There was definite bulging of the dura over the posterior half of the right cerebral hemisphere, with a small hemorrhagic area over the parietal region. The surface of the brain showed marked pallor, and the convolutions were flattened, with obliteration of fissures. No granularity of the fourth ventricle was noted. The vessels at the base of the brain were thin walled and free of any atheromatous process. The Spatz reaction of a piece of frontal cortex was negative.

In a horizontal section of the cerebral hemisphere, from the right parieto-occipital region, there was a massive cerebral hemorrhage, which had the shape of a long rectangle and measured about 6 by 2.5 cm. Its anterior pole rested against the caudal edge of the lenticular nucleus and extended backward to within a few millimeters of the occipital lobe. The hemorrhage had so increased the volume of the right cerebral hemisphere as to cause displacement of all midline structures on the left. Cross sections at various levels revealed that the hemorrhage had broken through the occipital cortex laterally. The rostral pole of this massive hemorrhage was exposed at the level of the mamillary bodies. In the right occipital lobe the entire white substance was disrupted and replaced by coagulated blood, so that only a thin shell of cortical substance remained. There were several punctate hemorrhages in the substance of the quadrigeminal plate. A section of the brain stem at the level of the trigeminal nerves displayed a large central hemorrhage in the tegmentum of the pons, which had broken into the fourth ventricle. There were two small hemorrhages in the left brachium pontis, which had broken into the subarachnoid space of the cisterna pontis. The spinal cord and posterior root ganglia did not display any gross lesions. The peripheral nerves presented evidence of congestion of the blood vessels.

Diagnosis.—The diagnosis was vascular syphilis, massive cerebral hemorrhage, pontile hemorrhage and cerebral compression.

Microscopic Examination of the General Body Organs.—The heart showed scattered infarctions, some old and fibrous, others recent and infiltrated with lymphocytes and plasma cells. The muscle fibers were fragmented and degenerated. Throughout, the smaller vessels showed perivascular lymphocytic collars, intimal proliferation, narrowing of the lumen and sometimes complete closure. The numerous infarctions appeared dependent on the obliterative endarteritis.

In the liver there were proliferation of bile ducts, increased capillary formation and small round cell infiltration. Hepatic arterioles showed perivascular lymphocytic collars and intimal proliferation. The surrounding liver cells were in various degrees of degeneration.

Besides evidence of early bronchopneumonia, the pulmonary vessels showed thickened walls, obliterative endarteritis, perivascular infiltration and neighboring areas of necrosis and scar formation.

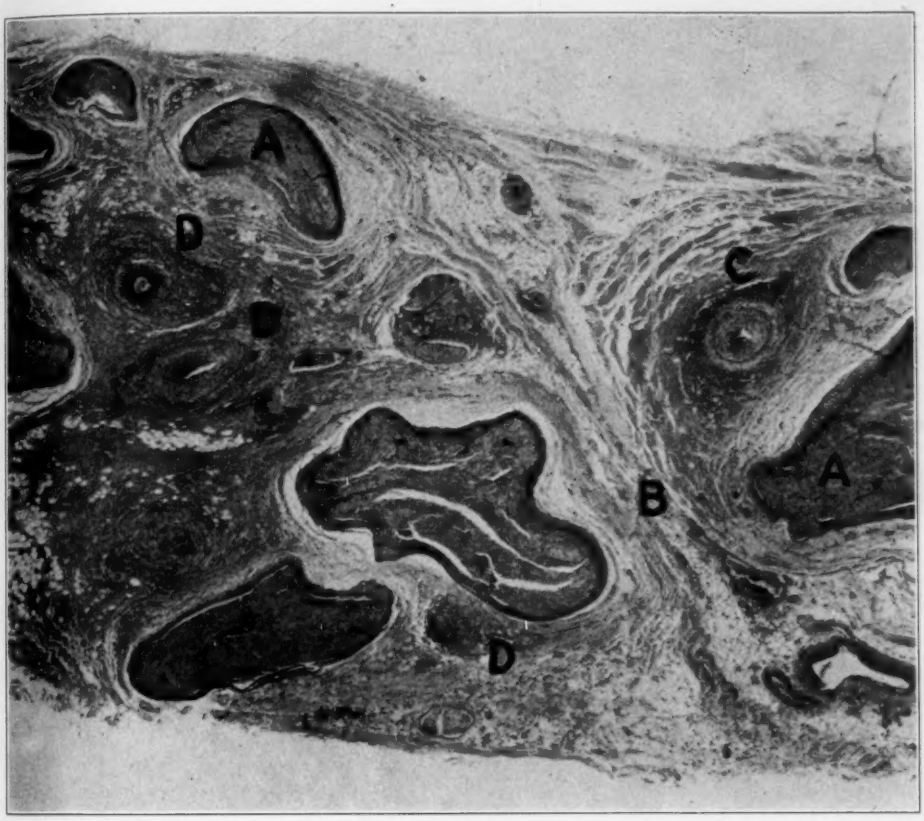

Fig. 1.—Cross section of the left brachial plexus. Hematoxylin and eosin stain; magnification, × 30.

Note the nerve bundles (*A*) and the increased connective tissue (*B*) between them. A small artery at *C* shows almost complete obliteration of the lumen, intimal proliferation and perivascular infiltration with lymphocytic cells. Similar changes of the arteries are seen at *D*.

Throughout a section of the pancreas were areas of necrosis, not all of which were due to postmortem autolysis. Some of the blood vessels were striking examples of proliferative endarteritis.

The kidneys, adrenal glands, spleen and testes showed similar pathologic changes, secondary to obliterative endarteritis of the smaller vessels. The thyroid gland showed no evidence of endarteritis.

Microscopic Examination of the Nervous System.—Sections were taken bilaterally from the brachial plexus, median nerve, sciatic nerve, femoral nerve, peroneal nerve, lumbar spinal ganglia, cervical, thoracic and lumbar regions of the spinal cord and frontal cortex. These were stained with hematoxylin and eosin, Davenport's stain for nerve fibers, the Weigert method for myelin sheaths and the Levaditi method for spirochetes.

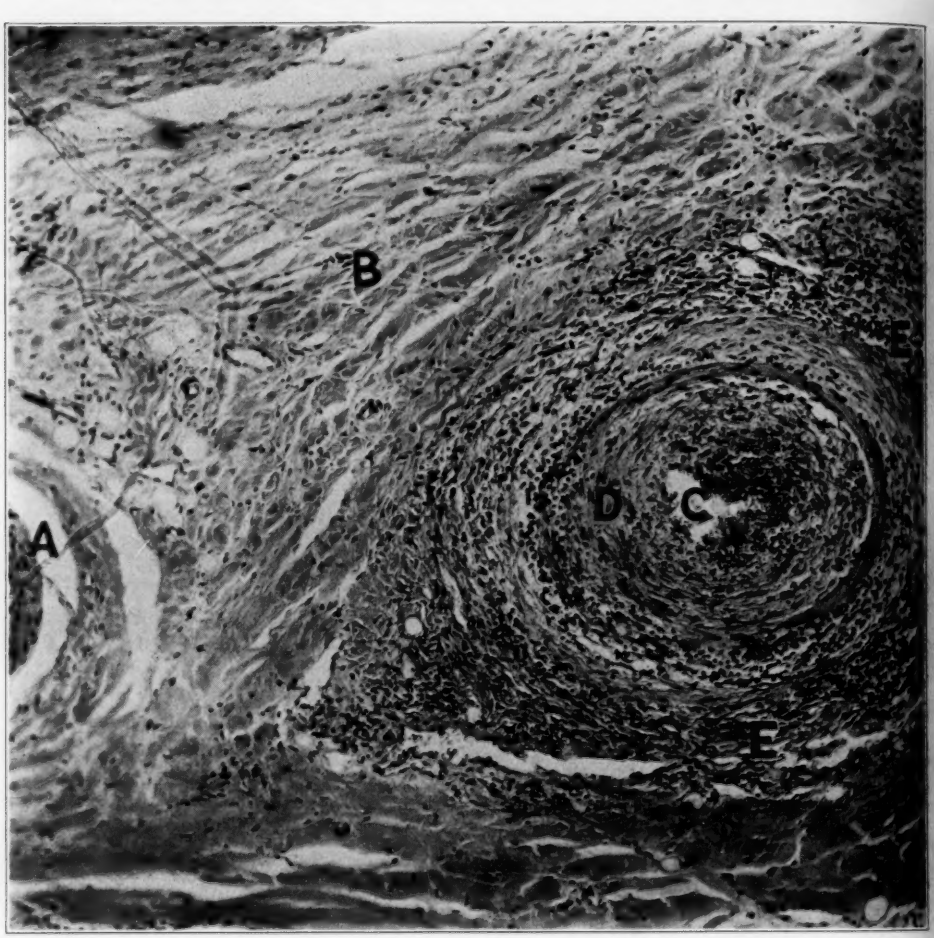

Fig. 2.—Magnification (×75) of the blood vessel (*C*) from the left brachial plexus, shown in figure 1. Hematoxylin and eosin stain.

This is a typical example of the syphilitic obliterative endarteritis and perivasculitis which can be seen in almost every organ throughout the body, indicating undoubtedly a hematogenous spread of the infection. Note the tip of a nerve bundle (*A*) and the increased connective tissue (*B*). The lumen of the blood vessel *C* is almost entirely obliterated by intimal proliferation (*D*). The perivascular collar of lymphocytes (*E*) is evident.

In spite of careful search, no unequivocal spirochetes were seen in any sections.

The pathologic changes in the peripheral nerves were essentially the same in all sections, varying only in degree. The nerves showed considerable proliferation

of connective tissue. In several areas there was hemorrhage into the perineurium. Almost every vessel in the connective tissue of the perineurium and endoneurium showed some degree of inflammatory change, with perivascular infiltration with lymphocytes and plasma cells and intimal proliferation tending to obliterative endarteritis. There was some round cell infiltration of the nerve fasciculi, but this was nowhere as marked as the perivascular inflammation. The neurilemma

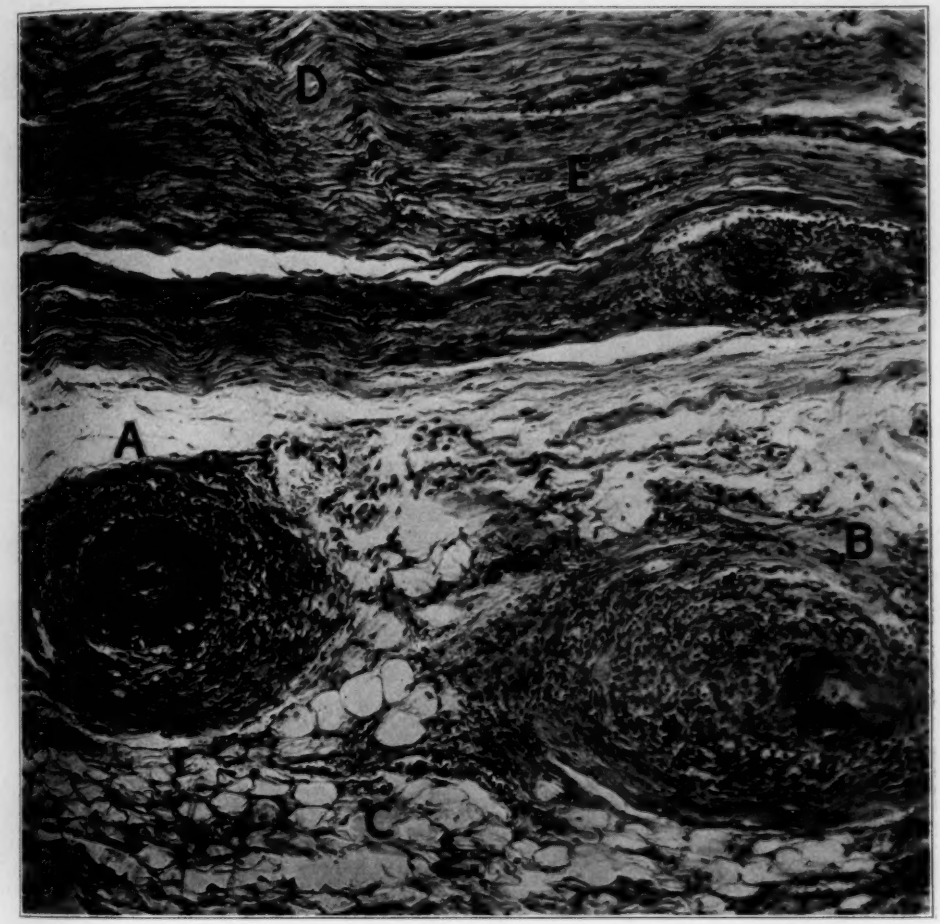

Fig. 3.—Right brachial plexus. Hematoxylin and eosin stain; magnification, × 70.

Note the two vessels (*A* and *B*) in the perineurium (*C*). These show the panarteritis and obliterative endarteritis distinctly. Nerve tissue is seen at *D*, and lymphocytic infiltration (*E*) is observed between the nerve fibers.

cells showed proliferation, and there was reduction in the number of nerve fibers stainable by silver, with fragmentation and degeneration of a widespread but spotty character. These areas of degeneration were usually in the vicinity of an obliterated vessel; however, this relation was not always evident. The Weigert

stain showed a corresponding degree of fragmentation and degeneration of the myelin sheaths. Occasional clumps of small round cells bearing no relation to a blood vessel were seen, and these could be considered miliary gummas. The areas surrounding obliterated blood vessels usually showed fibrosis and varying degrees of necrosis. The changes in the blood vessels were similar everywhere, differing in degree only and consisting of acute inflammatory panarteritis and

Fig. 4.—Right brachial plexus. Davenport stain for nerve fibers; magnification, × 400.

Note the swelling, fragmentation and sparsity of nerve fibers.

obliterative endarteritis, with subsequent degeneration of myelin sheaths and nerve fibers.

The cells of the spinal ganglia showed no unusual changes. However, in the arteries of the capsule of the ganglion and in the vessels of the attached dorsal root the panarteritis and perivascular inflammation were marked. The interference in the vascular supply to the ganglion had apparently not been sufficiently

severe to affect the ganglion cells. The Davenport and Weigert stains showed no definite areas of degeneration of either nerve fibers or myelin sheaths in the dorsal roots.

There were no gross lesions of the spinal cord. The anterior spinal artery showed definite thickening of the wall and a slight degree of subendothelial proliferation, but there was no round cell infiltration in or about the vessel. A vein and an artery on the dorsum of the cord were both completely obliterated by the endarteritic and endophlebitic changes associated with lymphocytic infiltration. Other small vessels in the spinal meninges showed changes varying from slight perivascular inflammation to dense infiltration of the walls of vessels and obliteration of the lumen. The spinal meninges were only slightly thickened,

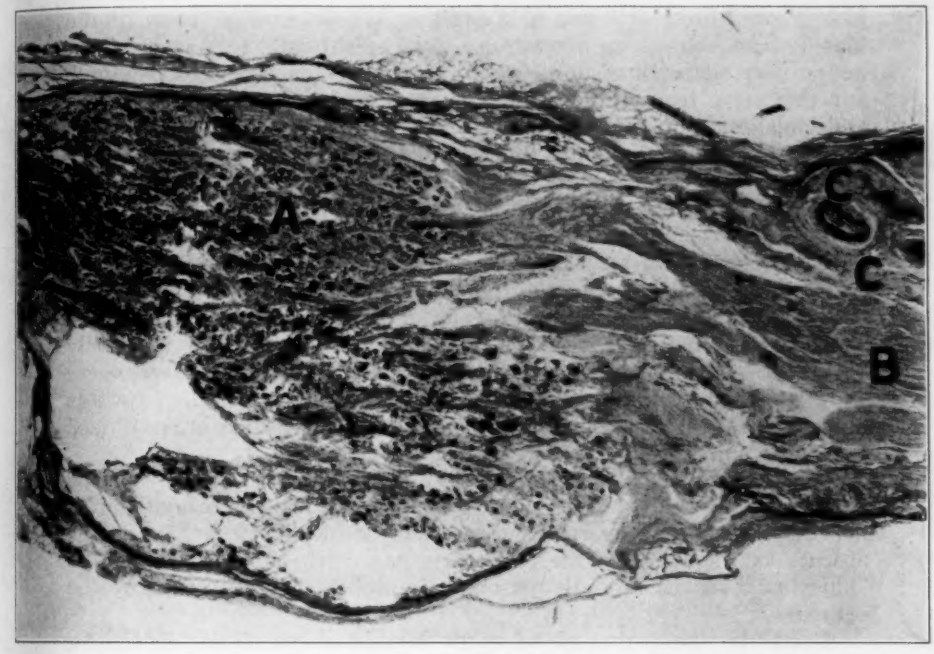

Fig. 5.—Right lumbar spinal ganglion (*A*) and dorsal root (*B*). Hematoxylin and eosin stain; magnification, × 30. Several vessels (*C*) show marked perivascular infiltration.

and the lymphocytic infiltration was mild, the inflammation for the most part being localized about the blood vessels. The sheaths surrounding the dorsal roots were thickened and densely infiltrated with round cells. Many of the blood vessels in the connective tissue of the roots showed marked panarteritic changes. The myelin sheath stain revealed no abnormality in the substance of the cord except slight demyelination in the fasciculus gracilis. This was less apparent in the thoracic region than in the cervical and lumbar portions.

The leptomeninges of the frontal cortex showed some fibrosis and moderate infiltration with small round cells. The cellular architecture was fairly well preserved. There was some proliferation of macroglia, and red cells were fairly conspicuous. No proliferation of blood vessels was noted. Mild endothelial hyperplasia was seen in a few vessels, and perivascular infiltration was uncommon.

COMMENT

The clinical picture of syphilitic polyneuritis does not differ essentially from that of toxic and infectious neuritis, although fever is usually absent in the toxic type. Sharp, lancinating, boring pains along the course of the nerve, tenderness on pressure over the nerve trunk or muscle, motor weakness and paralysis, areas of loss of sensation, loss of deep reflexes and muscular atrophy may occur. Depending on the nerve or nerves involved, the syndrome may be purely motor or purely sensory or may show mixed motor and sensory signs. Paresthesias, hyperesthesia and tingling and numbness in the distal portions of the extremities may occur. The onset is usually gradual, and the disease may run a subacute or chronic course. There is almost always a definite history or definite evidence of a positive Wassermann reaction of the blood. The Wassermann reaction of the spinal fluid may or may not be positive, depending on whether the meninges are involved, and, for the same reason, there may or may not be an increase in cells and globulin.

At the onset of the illness this patient suffered acute parotitis. While rare, peripheral neuritis and meningoencephalitis after acute parotitis [9] have been known to occur, but are usually recoverable. We know of no reports in the literature describing the pathologic changes of the peripheral nerves in this condition.

Prior to the development of neuritic symptoms, this patient received neoarsphenamine and a bismuth preparation. A trivalent arsenical, such as neoarsphenamine, rarely causes peripheral neuritis, and then only with high doses, which this patient did not receive. Moreover, there were no other toxic manifestations of arsphenamine poisoning, such as cutaneous symptoms or hemorrhagic encephalitis, which is characterized by edema and punctate hemorrhages.

Since bismuth has a low toxicity, the possibility of polyneuritis resulting from the drug in this case is slight. Cases of bismuth polyneuritis have been reported, however (Critchley,[10] Becker [11]). The absence in the present case of other signs, such as stomatitis and a "blue line," makes bismuth poisoning improbable as the cause of the neuritis.

Certainly, the pathologic changes in this case did not indicate a parenchymatous degenerative neuritis, as the inflammatory response was far greater proportionately than the degeneration of nerve fibers or myelin sheaths. The condition was, rather, a perineuritis, endoneuritis or interstitial neuritis secondary to pathologic changes in the blood vessels of the nerves. The fundamental pathologic process was panvasculitis associated with perivascular infiltration, infiltration of the walls of the blood vessels and intimal proliferation, which was sometimes so severe as to lead to occlusion of the lumen. Most of this inflammatory process

9. Etienne, G., and Gerbaut, P.: Polynévrites ourliennes, Rev. méd. de l'est **58**:562, 1930. Collens, W. S., and Rabinowitz, M. A.: Mumps Polyneuritis: Quadriplegia with Bilateral Facial Paralysis, Arch. Int. Med. **41**:61 (Jan.) 1928.

10. Critchley, M.: Bismuth Polyneuritis, Brit. J. Ven. Dis. **2**:83, 1926.

11. Becker, S. W.: Herpes Zoster and Polyneuritis Following the Administration of Bismuth, Am. J. Syph. **16**:313, 1932.

existed in and about the blood vessels, but occasionally clumps of lymphoid and plasma cells were observed which bore no relation to blood vessels; these were to be considered as miliary gummas. The degeneration of nerve fibers and myelin sheaths was secondary to interference with the nutrition of the nerves resulting from the changes in the blood vessels, which consisted of acute arteritis or phlebitis and obliterative endarteritis or endophlebitis. This pathologic process occurred not only in the nervous system but throughout most of the body organs and indicated a hematogenous spread of the infection.

Margulis [7] placed much emphasis on the changes in the muscles and preferred to call this condition polyneuromyositis. Logically, however, there is no more reason to emphasize the changes in the muscles than those in the heart, kidney and adrenal gland. The clinical symptoms will be most marked in organs in which the vascular disease interferes most with function. Syphilitic polyneuritis is the manifestation of only one localization of a process which has spared few of the body organs.

The polyneuritis resulting from syphilitic vascular disease is different from the neuritis which is produced secondarily by pressure from a gumma or syphilitic osteitis or periostitis. These lesions, moreover, are more apt to produce mononeuritis than polyneuritis.

It is to be regretted that the spirochetes could not be demonstrated in the peripheral nerves. The diagnosis of the syphilitic origin in this case must depend on the clinical history and examination, the positive serologic reactions of the blood and spinal fluid and the pathologic evidence that the clinical symptoms were due to panvasculitis, with infiltration in and about the walls of the blood vessels, associated with intimal proliferation, leading to obliterative endarteritis and endophlebitis. This is a characteristic lesion of syphilis.

SUMMARY

1. Syphilitic polyneuritis may occur in all stages of syphilis, and its occurrence is not limited to the early stages.

2. One case is reported, together with the pathologic observations.

3. The clinical signs of peripheral neuritis of syphilitic origin do not differ from those of nonsyphilitic origin.

4. The Wassermann reaction of the blood is usually positive, and that of the spinal fluid may or may not be positive.

5. The fundamental pathologic process is panvasculitis with lymphocytic and plasma cell infiltration in and about the walls of the blood vessels, associated with intimal proliferation, leading to obliterative endarteritis and endophlebitis.

6. This pathologic process is spread by the hematogenous route and may occur in any body organ, with the clinical picture of peripheral neuritis resulting from its localization in the peripheral nerves.

7. The prognosis in most cases is favorable if early, regular and sufficient antisyphilitic therapy is given.

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FATAL HYPOGLYCEMIA

A Clinicopathologic Study

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The use of insulin in the treatment of diabetes mellitus and its recent employment in the therapy of schizophrenia and other conditions carry the possibility of undesirable and dangerous complications, the one most feared being a state of coma from which recovery does not occur. The effects on the nervous system of hypoglycemic states of long standing are not completely understood, but the increasing number of studies along this line give evidence that definite progress is being made. We have had the opportunity to study a case with special methods which, it is hoped, will add to information relative to the pathologic picture.

SUMMARY OF THE LITERATURE

Olmsted and Logan [1] reported on the possible connection between the lowering of blood sugar and anoxia of the brain. Kleitman and Magnus [2] produced insulin convulsions in rabbits under conditions of artificial respiration and concluded that the convulsions were not secondary to generalized anoxemia. Olmsted and Taylor [3] expressed the belief that hypoglycemia reduced the oxidative processes of the brain. The work of Holmes [4] tended to prove that the oxygen consumption of brain tissue was directly related to the presence of dextrose and that the oxygen uptake of gray matter of animals after injections of insulin was less than that of normal animals used as controls. Moldavsky and Gellhorn [5] found in dogs that the elevation in blood pressure occurring during the inhalation of 6.2 per cent oxygen for three minutes increased in proportion to the fall of blood sugar obtained after intravenous injection of large doses of insulin. The investigations of Dameshek and

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* Rockefeller Traveling Research Fellow (1938).

From the Department of Neurology, the Harvard Medical School, and the Neurological Unit, the Boston City Hospital, Boston.

1. Olmsted, J. M. D., and Logan, H. D.: The Effect of Insulin on the Central Nervous System, and Its Relation to the Pituitary Body, Am. J. Physiol. **66**:437, 1923.

2. Kleitman, N., and Magnus, R.: Zur Wirkung des Insulins auf das Zentralnervensystem, Arch. f. d. ges. Physiol. **205**:148, 1924.

3. Olmsted, J. M. D., and Taylor, A. C.: Effect of Insulin on the Blood: I. Changes in Oxygen Saturation, Percentage Hemoglobin and Oxygen Capacity, Am. J. Physiol. **69**:142, 1924.

4. Holmes, E. C.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

5. Moldavsky, L., and Gellhorn, E.: On the Relationship Between Hypoglycemia and Anoxemia, Proc. Soc. Exper. Biol. & Med. **36**:92, 1937.

Myerson [6] on human beings revealed that the uptake of oxygen by the brain varied inversely to the severity of the insulin reaction. They concluded that the neurologic symptoms of the insulin reaction might be due to the effects of anoxemia on brain tissue. The work of Wortis [7] on animals showed that insulin diminished the oxygen consumption of brain tissue. A more recent publication by the same author [8] emphasized that the depression of brain function during hypoglycemia was due to anoxemia and that in prolonged depression of metabolic processes in the brain irreversible changes in this organ occurred. Further experiments by Ingraham, Moldavsky and Gellhorn [9] indicated that during insulin hypoglycemia in dogs the elevation in blood pressure occurring during inhalation of low concentrations of oxygen increased as the blood sugar fell. Dextrose given intravenously diminished the blood pressure response to oxygen deficiency. Another report by Gellhorn [10] showed that a mild degree of anoxia produced in a low pressure chamber intensified the effects of insulin in the production of convulsions.

Histopathologic changes in hypoglycemia have been intensively studied in animals and in man. Schmid [11] submitted rabbits to repeated insulin shocks followed by the administration of dextrose. Changes in ganglion cells and glial elements, together with marked capillary hyperemia, were noted. The experiments of Stief and Tokay [12] on rabbits and dogs caused severe changes in ganglion cells, with extreme widening of meningeal and cerebral vessels and subarachnoid hemorrhages after daily injections of insulin in increasing amounts. Schereschewsky and his associates [13] observed pericapillary hemorrhages with changes in ganglion cells in dogs which had received massive doses of insulin. Sherrill and MacKay [14] made the important observation that

6. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: Mechanism of the Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935.

7. Wortis, S. B.: Respiratory Metabolism of Excised Brain Tissue: II. The Effects of Some Drugs on Brain Oxidations, Arch. Neurol. & Psychiat. **33**:1022 (May) 1935.

8. Wortis, S. B.: Effects of Insulin, Metrazol and Camphor Convulsions on Brain Metabolism, New York State J. Med. **38**:1015, 1938.

9. Ingraham, R. C.; Moldavsky, L., and Gellhorn, E.: On the Relation Between Hypoglycemia and Anoxemia, Am. J. Physiol. **119**:341, 1937. Gellhorn, E.; Ingraham, R. C., and Moldavsky, L.: The Influence of Hypoglycemia on the Sensitivity of the Central Nervous System to Oxygen Want, J. Neurophysiol. **1**: 301, 1938.

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11. Schmid, H.: L'histopathologie du choc insulinique, Ann. méd.-psychol. (pt. 2) **94**:658, 1936.

12. Stief, A., and Tokay, L.: Beiträge zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434, 1932.

13. Schereschewsky, N. A.; Mogilnitzky, B. N., and Gorjaewa, A. W.: Zur Pathologie und pathologischen Anatomie der Insulinvergiftung, Endokrinologie **5**: 204, 1929.

14. Sherrill, J. W., and MacKay, E. M.: Deleterious Effects of Insulin Shock, Proc. Soc. Exper. Biol. & Med. **36**:515, 1937.

when the state of shock was maintained in dogs for twenty-four hours or longer it was impossible to resuscitate the animals. After animal experimentation, Weil and his co-workers [15] expressed themselves in favor of the explanation of "intracellular anoxia," or inability to utilize oxygen in the presence of large doses of insulin, as the cause of the pathologic changes in the brain.

There is no great uniformity of opinion regarding the changes in the reported cases of fatal hypoglycemia in man. Wohlwill [16] described cellular changes but no vascular lesions. Bowen and Beck [17] observed extensive swelling of the brain, the sulci being obscured and the gyri greatly enlarged and flattened. Edema and hyperemia of the brain were marked, the ventricles being diminished in size and the brain weighing 1,535 Gm. In the majority of cases of Ehrmann and Jacoby [18] there were subarachnoid and small cerebral hemorrhages. Cellular changes with perivascular hemorrhages were reported by Terbrüggen,[19] de Morsier and Mozer [20] and Moersch and Kernohan.[21] Baker and Lufkin [22] reported 3 cases in which numerous old and new hemorrhages were present, the authors remarking that the hemorrhages were most numerous in patients who had the most severe convulsive seizures. Brains of rabbits in which repeated hypoglycemic convulsions were produced showed no alterations of pathologic significance. In the case of Terplan [23] there was extreme edema of the brain with injection of the vessels, together with cellular changes.

METHOD

The study of lesions of the human central nervous system by means of the benzidine stain (Campbell, Alexander and Putnam; [24] Alexander

15. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

16. Wohlwill, F.: Ueber Hirnbefunde bei Insulin-Ueberdosierung, Klin. Wchnschr. **7**:344, 1928.

17. Bowen, B. D., and Beck, G.: Insulin Hypoglycemia, Ann. Int. Med. **6**: 1412, 1933.

18. Ehrmann, R., and Jacoby, A.: Ueber Blutungen bei mit Insulin behandelten Komafällen, Klin. Wchnschr. **4**:2151, 1925.

19. Terbrüggen, A.: Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome, Beitr. z. path. Anat. u. z. allg. Path. **88**: 37, 1932.

20. de Morsier, G., and Mozer, J. J.: Lésions cérébrales mortelles par hypoglycémie, Ann. de méd. **39**:474, 1936.

21. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat. **39**:242 (Feb.) 1938.

22. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190 (Feb.) 1937.

23. Terplan, K.: Changes in the Brain in a Case of Fatal Insulin Shock, Arch. Path. **14**:131 (July) 1932.

24. Campbell, A. C. P.; Alexander, L., and Putnam, T. J.: Vascular Pattern in Various Lesions of the Human Central Nervous System, Arch. Neurol. & Psychiat. **39**:1150 (June) 1938.

and Putnam [25]) is particularly applicable to conditions in which congestion of the brain is suspected. By the use of this technic, in addition to routine stains, we were able to obtain a much more comprehensive picture than before of the neuropathologic changes in a case of fatal hypoglycemia, the clinical report of which follows.

REPORT OF A CASE

History.—A. W., a white man aged 58, was admitted on Feb. 10, 1938, with the complaint of an infection of the right great toe, of four days' duration. Twelve years previously he had had polyuria and polydypsia; a diagnosis of diabetes mellitus was established; he was given insulin, 15 units per day, and a diet was prescribed, which he did not follow strictly. He had taken no insulin for four years previous to admission to the hospital. There had been a gradual loss of weight over a period of years, with some swelling of the ankles. Four days before admission a blister on his right great toe became infected, and hospital treatment was advised.

Examination.—The patient was thin and pale, but in no apparent distress. The temperature was 98 F., the pulse rate 80 per minute and the respiratory rate 12 per minute. His pupils were small and slightly irregular and reacted rather sluggishly to light. His tongue was dry and bright red. The chest showed nothing unusual. The blood pressure was 130 systolic and 60 diastolic. The edge of the liver was 2 fingerbreadths below the right costal margin. At the base of the right great toe was a purplish raised area from which yellowish pus exuded. The right foot was swollen. Pulsation of the dorsalis pedis artery was barely perceptible on the right. Examination of the urine revealed: specific gravity, 1.025; a trace of albumin; a strongly positive reaction for sugar, and a negative reaction for acetone. Examination of the blood revealed: hemoglobin concentration, 80 per cent; red blood cells, 3,250,000; white blood cells, 20,000 per cubic millimeter; Hinton reaction, negative; nonprotein nitrogen, 37 mg., and sugar, 300 mg. per hundred cubic centimeters.

Course.—Diabetic management was instituted, with a diet that consisted of 125 Gm. of carbohydrate, 59 Gm. of protein and 79 Gm. of fat daily. Thirty units of insulin was given three times a day. Four days later the blood sugar was 385 mg. per hundred cubic centimeters, at which time the medication was changed to 20 units of protamine zinc insulin before breakfast, together with 20 units of regular insulin. Forty units of insulin was given before lunch and supper, as before. The infection about the right great toe spread slowly, cultures of the wound revealing Staphylococcus aureus and Staphylococcus albus. On the sixth day of his stay in the hospital the blood sugar had reached 93 mg. per hundred cubic centimeters. That night he had an insulin reaction which was characterized by clouding of consciousness and profuse perspiration, from which he recovered almost immediately when given orange juice. On the following evening another reaction occurred, but this time there was no response to orange juice. One and one-half hours later 40 units of insulin was given, together with 1,000 cc. of 5 per cent dextrose, but the patient did not immediately regain consciousness. Another injection of dextrose—50 cc. of a 50 per cent solution—

25. Alexander, L., and Putnam, T. J.: Pathologic Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**:471, 1938.

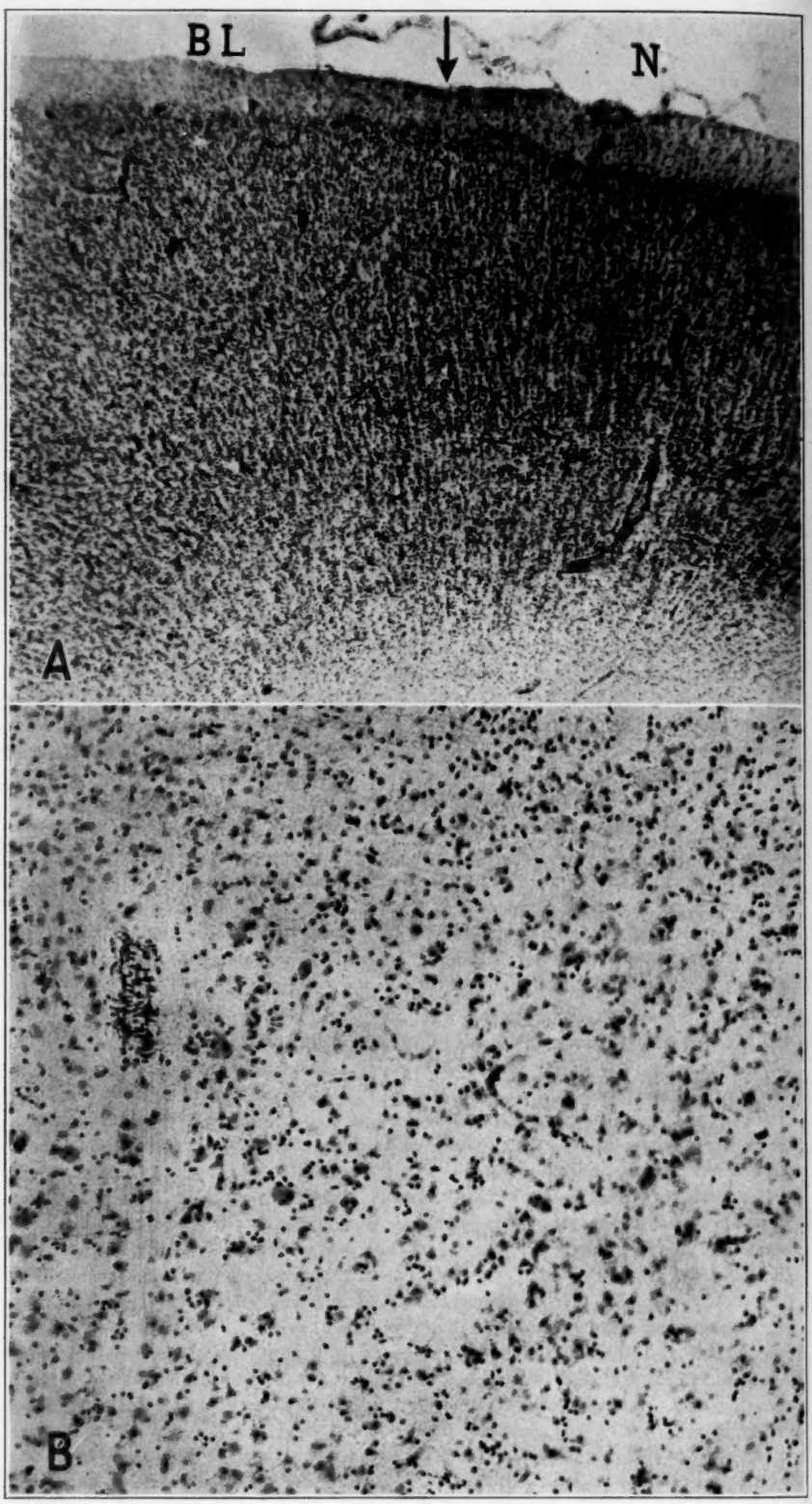

Fig. 1.—Photomicrographs of a section from the postcentral region. Nissl stain. *A* is low power view (× 31.5). The arrow indicates the border between the focus of blanching (*Bl*) and the adjacent normal cortex (*N*). *B* is a greater enlargement (× 140) of part of the focus of blanching shown in *A*. Note the acute ischemic degeneration of ganglion cells, while the number and nuclear staining of oligodendroglia cells have remained unaltered.

was given, with the result that he awoke and responded normally; once more he lapsed into an unconscious state in which perspiration was profuse and respirations were labored. The blood sugar at this time was zero. No convulsions, however, occurred. Repeated intravenous injections of dextrose were given;

Fig. 2.—Photomicrograph of a section from the central region, including the second to the sixth layer of the cerebral cortex (in the upper half and at the lateral margin of the figure) and the convolutional white matter (in the central part of the lower half and at the lower margin of the figure). Benzidine stain; × 52. Note the dilatation and irregular variation in caliber of the vascular bed.

in addition, he received a total of 100 units of insulin throughout the morning, the blood sugar at one time being 465 mg. per hundred cubic centimeters. The coma deepened, and the patient died on the morning of the ninth day in the hospital, after having been in shock for twenty-eight hours.

Fig. 3.—Photomicrograph of a section from the anteroventral part of the caudate nucleus. Benzidine stain; × 52. Note the irregular dilatation of the capillary bed and perivascular hemorrhages about the supracapillary vessels.

Autopsy.—This was performed twenty-nine hours after death. The gross observations included moderate atheromatous changes in the coronary arteries;

atherosclerosis of the aorta; pulmonary congestion and edema, and moderate cellulitis of the right foot.

Brain: The dura was tense. On incision of the dura the pial vessels were seen to be hyperemic. The convolutions were flattened, and the sulci were narrowed. The brain weighed 1,450 Gm. The vessels at the base showed no gross evidence of arteriosclerosis. Numerous frontal sections showed marked hyperemia of the gray and white matter, the gray matter being distinctly brownish. The

Fig. 4.—Homogeneous, amorphous, fibrinous thrombus in an arteriole of the fourth order in the ventrolateral nucleus of the thalamus. Bodian stain; × 600.

white matter had a somewhat grayish appearance except for the U fibers, which stood out prominently, owing to their unaltered white color. There was particularly severe congestion of the cornu ammonis. Numerous small hemorrhages were seen grossly in the dentate nuclei. Extreme congestion was also noted in the spinal cord.

Microscopic Appearance.—Sections from representative areas were stained by the Lepehne-Pickworth, Weigert-Pal, Marchi, Nissl, Masson and Bodian methods, with Weigert's fibrin stain and with hematoxylin and eosin. In the frontal, occipital

and temporal regions, including the cornu ammonis, the cortical architecture was normal. A number of the larger intracerebral vessels showed fibrosis with a slightly increased number of adventitial cells, but not to any degree that could be considered unusual in a person of the age of the patient. Some of the vessels of the fourth order were densely filled with blood, others with polymorphonuclear leukocytes. In some places the meninges showed a moderate increase in histiocytic elements. In the gray matter of the central and upper parietal regions, however,

Fig. 5.—Homogeneous, amorphous, fibrinous thrombus in a venule of the third order in the ventrolateral nucleus of the thalamus. Weigert's fibrin stain; × 1,000 (oil immersion).

there were foci of early blanching, one of them involving altogether 12 mm. of the cortical ribbon located at the depth of the valley between the posterior central convolution and the adjacent anterior surface of the superior parietal lobule (area 7). There were similar, smaller lesions elsewhere in the central and upper parietal regions. Under a low power lens the light-staining quality of these foci of blanching was conspicuous; the architectural borders between the various cortical layers were wiped out, except between the first and the second layer

(fig. 1*A*); in addition, the sharpness of delimitation of the cortex from the underlying white matter was diminished. Under a higher magnification pale staining and shrinkage of the cytoplasm of ganglion cells, associated with pyknosis of their nuclei in all layers, were conspicuous, while only the oligodendroglia

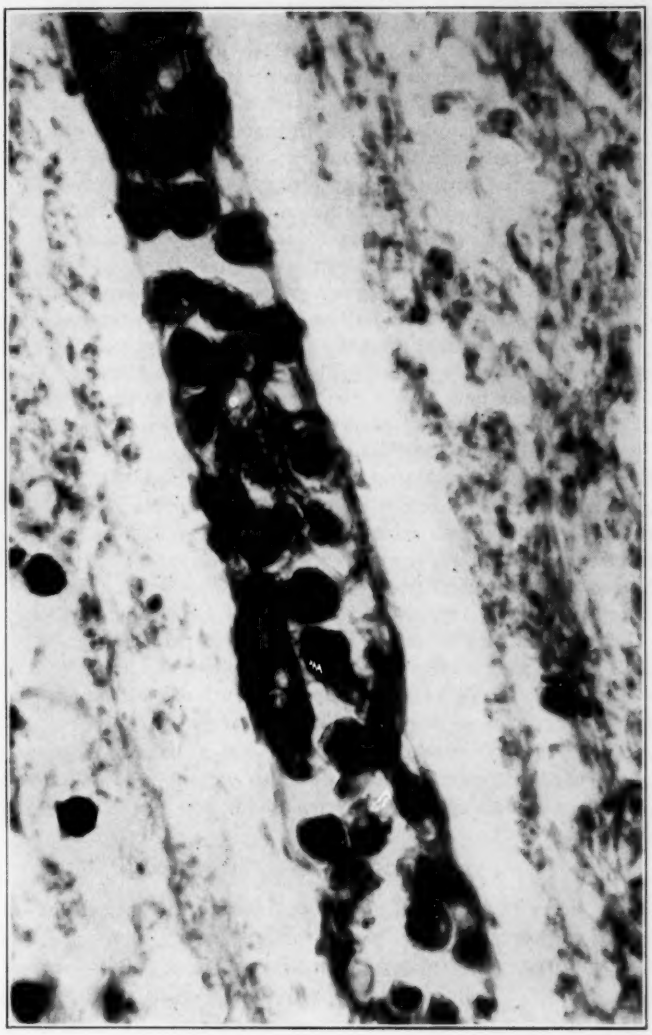

Fig. 6.—Early fibrinous, cellular thrombus (white blood cells in a scanty meshwork of fibrin, "white stasis" ?) in a venule of the third order in the subcortical white matter of the postcentral region. Masson's trichrome stain; × 1,100 (oil immersion).

cells appeared to stand out as well stained against the otherwise relatively decolorized background (fig. 1 *B*). This picture might convey the erroneous impression of an increase in glia cells, but in reality they appeared to be more prominent only because of the loss of ganglion cells. In some instances the inner layers were more severely involved than the outer layers, but in most cases the entire width of the cortical ribbon was affected. Nissl specimens also demonstrated that the perivascular hemorrhages did not usually occur in vessels showing fibrosis, but seemed to have a predilection for unaffected vessels. This phenomenon appeared to indicate that the occurrence of hemorrhages was independent of the slight proliferative changes in the adventitia. Marchi preparations showed no degeneration of myelin. Myelin sheath stains revealed no actual degeneration of myelin, but throughout the brain the sheaths appeared to be pushed apart as though by interstitial edema, thereby giving some areas, particularly the convolutional white matter, a diffusely lightened appearance. The dilated interstices were occupied by swollen oligodendroglia cells; this phenomenon was most conspicuous in silver preparations, but seen with other stains as well. Lepehne-Pickworth preparations for the vascular pattern were striking with respect to the extreme degree of irregular dilatation and congestion of vessels of all sizes (fig. 2). This appearance was present on the arterial as well as on the venous side. Perivascular hemorrhages were in evidence in the striatum (fig. 3), the anterior perforated substance, the cornu ammonis and the nucleus of the vagus nerve. There was a great deal of irregular variation in caliber, especially of the capillary bed (figs. 2 and 3). There were occasional small, beadlike deformities, but most of the variations in caliber were gradual.

Sections stained with Masson's trichrome technic, with Weigert's stain for fibrin and with Bodian's silver stain showed that numerous vessels in the diencephalon and a smaller number in the cortical gray and subcortical white matter were occluded by thrombi of several types. Fibrinous, homogeneous, amorphous thrombi in arterioles and venules (figs. 4 and 5), as well as fibrinous, cellular thrombi (that is, thrombi consisting of curved strands of fibrin with admixture of red and white blood cells) were observed. In addition, instances were seen in which numerous white blood cells were enmeshed in scanty threads of fibrin, a picture which may be interpreted as early thrombosis, or as "white stasis" (fig. 6).

Silver stains (Bodian) showed the axis-cylinders to be pushed apart as though by interstitial edema, a picture which was also present in myelin sheath preparations. Individual axis-cylinders did not show any significant abnormalities, however.

COMMENT AND CONCLUSIONS

The case described illustrates the pathologic alterations in the brain resulting from hypoglycemic shock of twenty-eight hours' duration. These observations confirm and amplify those of other authors. Of particular interest is the marked degree of vascular disturbance, as illustrated by the Lepehne-Pickworth preparations. The association of dilatation of vessels with irregular variations in caliber and small perivascular hemorrhages, in addition to the occurrence of numerous thrombi, tends to indicate, in the light of the work of Campbell, Alexander and Putnam,[26] that a marked degree of circulatory dis-

26. Campbell, Alexander and Putnam.[24] Alexander and Putnam.[25]

turbance with "peristasis" [27] and, finally, stasis of blood occurred in the brain of this patient. The changes are not specific, since similar changes can be observed in cases of carbon monoxide poisoning, electrical injury and occlusion of large arteries of the sixth and seventh orders. The parenchymal changes (foci of blanching and edema) are secondary to the circulatory disturbance and are undoubtedly due to local and general anoxia. It is of interest to note that these were limited to the central and upper parietal regions, which are the areas most regularly involved by disturbances interfering with the venous return from the brain.

SUMMARY

The clinical and pathologic observations on a diabetic patient who received large doses of insulin and remained in hypoglycemic shock without convulsions for twenty-eight hours before death are reported.

The pathologic changes are: irregular dilatation of intracerebral vessels, indicating varying degrees of sluggish flow; multiple thrombi and perivascular extravasations, notably in the basal ganglia and medulla oblongata, but involving other areas as well; foci of blanching in the central and upper parietal regions of the cortex, and interstitial edema, with swelling of oligodendroglia cells in the cerebral white matter.

Evidence is presented to support the anoxic theory of hypoglycemic shock.

27. Ricker, G., and Regendanz, P.: Beiträge zur Kenntnis der örtlichen Kreislaufstörungen, Virchows Arch. f. path. Anat. **231**:1, 1921.

SPECIAL ARTICLE

INTRACRANIAL ANEURYSMS

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Intracranial aneurysm is an old subject with renewed interest to physicians and surgeons. The literature is extensive. From 407 articles published before Jan. 1, 1938 we have assembled 1,125 cases of saccular aneurysm of the arteries at the base of the brain verified by autopsy or operation. Among the authors of these articles are many of the great names of medicine. The literature dates from 1761, when Morgagni, of Padua, described dilatations of the posterior branches of both carotid arteries. Ruptured intracranial aneurysm was first reported in 1778 by Biumi, of Milan, who gave a clear clinical description of the disease now called "spontaneous subarachnoid hemorrhage" and described the ruptured aneurysm observed at autopsy. The next significant contribution was made by Gull, of Guy's Hospital, in 1859. In a modern scientific article he reviewed the literature and reported 6 cases with clinical and postmortem observations. From this study he concluded:

> Whenever young persons die with symptoms of ingravescent apoplexy, and after death large effusion of blood is found, especially if the effusion be over the surface of the brain in the meshes of the pia mater, the presence of an aneurysm is probable.

Albright's stimulating article in 1929 has attracted much attention. Moniz, of Lisbon, provided an ingenious means of localizing aneurysms by his angiographic technic. Dott, of Edinburgh, has recently reported several cases in which the condition was cured by surgical means.

To the extensive literature we are adding the reports of 2 cases which illustrate points of interest. In case 1 there was an anomaly of the circle of Willis with a ruptured aneurysm, extensive arteriosclerosis and syphilitic aortitis. In case 2 a ruptured aneurysm of the internal carotid artery involved the third cranial nerve.

Read at a meeting of the Boston Society of Psychiatry and Neurology, May 19, 1938.

ANALYSIS OF THE DATA IN 1,125 CASES FROM THE LITERATURE

From the literature we have compiled 1,125 cases of intracranial aneurysm. We have analyzed these cases as to: (1) artery involved by the aneurysms, (2) age, (3) sex, (4) artery involved by the ruptured aneurysm, and (5) pathologic changes in the arteries at the base of the brain.

1. *Artery Involved by the Aneurysms.*[1]—Four hundred and eighty-nine, or 48 per cent, of the aneurysms were located on the internal

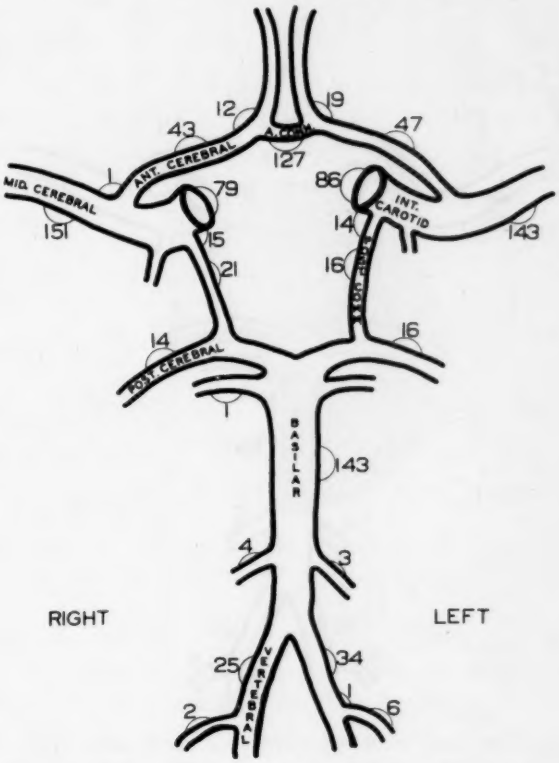

Chart 1.—Location of intracranial aneurysms in 1,023 cases.

carotid or the middle cerebral artery; 156, or 15 per cent, on the anterior communicating artery, and only 286, or 28 per cent, posterior to the internal carotid arteries. Chart 1 shows the location of 1,023 aneurysms for which there was a statement as to the artery involved.

2. *Age of the Patient.*—Aneurysms occurred at all ages. The youngest patient was 1½ years of age; the oldest, 87. Of 545 patients whose ages were stated, 54 per cent were over 40 years of age, and 35 per cent

1. In the appendix the cases are listed according to the artery involved.

were from 21 to 40. Only 11 per cent were under 20, which is contrary to a common clinical belief that cerebral aneurysms are most frequent in young persons. The relative frequency of cases in these three age periods is shown in chart 6.

3. *Sex of the Patient.*—Five hundred and seventy-four patients were female, and 519 were male.

4. *Artery Involved by the Ruptured Aneurysms.*—Ruptured aneurysms were three times as frequent on the anterior part of the circle of

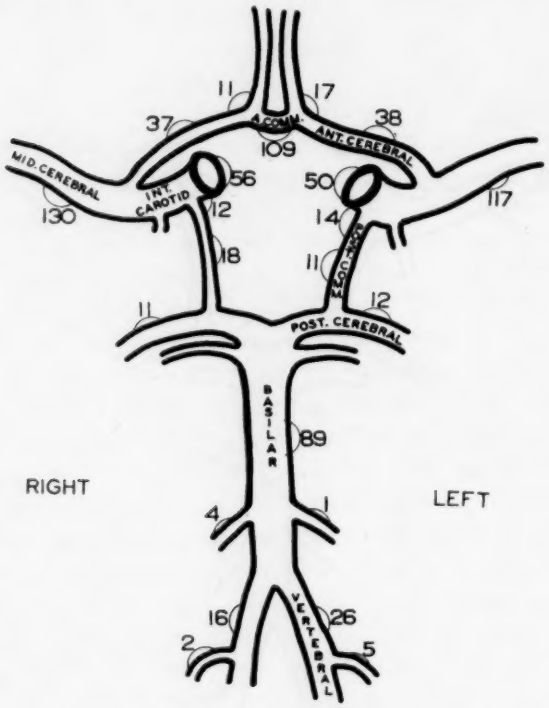

Chart 2.—Location of ruptured intracranial aneurysms in 786 cases.

Willis as on the posterior part. In 862 cases the aneurysm was ruptured, and in 786 of these there was a statement as to the artery on which the aneurysm was located. As shown in chart 2, 48 per cent of the ruptured aneurysms were on the internal carotid or the middle cerebral artery; 17 per cent were on the anterior communicating artery, and only 24 per cent were posterior to the internal carotid arteries.

5. *Pathologic Changes in the Arteries.*—The appearance of the arteries at the base of the brain was described in 572 cases. In 385

cases, or 67.3 per cent, the vessels showed pathologic changes; in the remaining 177 cases, or 32.7 per cent, the vessels were described as normal, the aneurysms being commonly referred to as congenital. In 283 of the 385 cases in which the vessels were morbid, there were sclerotic arteries; in 70, mycotic emboli, and in 32, syphilitic arteries. Chart 3 shows that cases in which the vessels were morbid were twice as frequent as those in which they were normal. In 49.5 per cent of the 572 cases in which the vessels were described there were sclerotic arteries; in 12.2 per cent, mycotic emboli, and in 5.6 per cent, syphilitic arteries.

The age distribution of the patients with normal vessels and those with the various types of morbid vessels is shown in charts 4, 5 and 6. In 545 cases both the age of the patient and the appearance of the arteries were given.

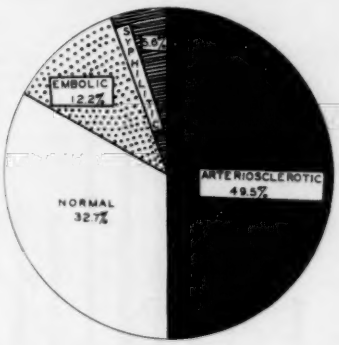

Chart 3.—Pathologic changes in the arteries in 572 cases of intracranial aneurysms taken from the literature.

(*a*) Age Distribution of Patients with Morbid and with Normal Vessels: Chart 4 shows that the number of patients with normal vessels equaled the number with morbid vessels only between the ages of 20 and 35. At all other ages, even under 20, there were more patients with morbid vessels than with normal vessels.

(*b*) Age Distribution of Patients with Sclerotic Arteries, Mycotic Emboli and Syphilitic Arteries: Thirty-two patients with syphilitic arteries were from 20 to 75 years of age. In 70 cases of mycotic emboli the patients for the most part were young and had bacterial endocarditis. In 274 of 545 cases there was arteriosclerosis. Chart 5 shows strikingly the large number of cases of arteriosclerosis in young patients.

In chart 6 the relative frequency in early, middle and late life of cases in which the vessels were normal and cases in which there were sclerotic arteries, mycotic emboli and syphilitic arteries is illustrated.

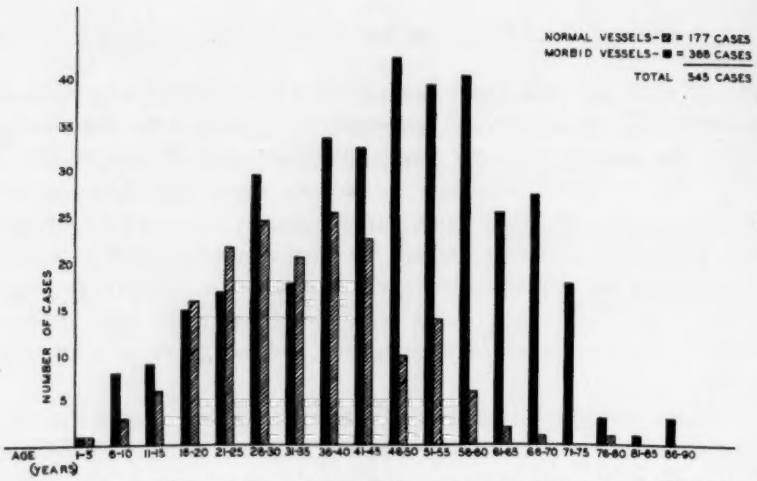

Chart 4.—Condition of the blood vessels, with age incidence, in 545 cases of intracranial aneurysms.

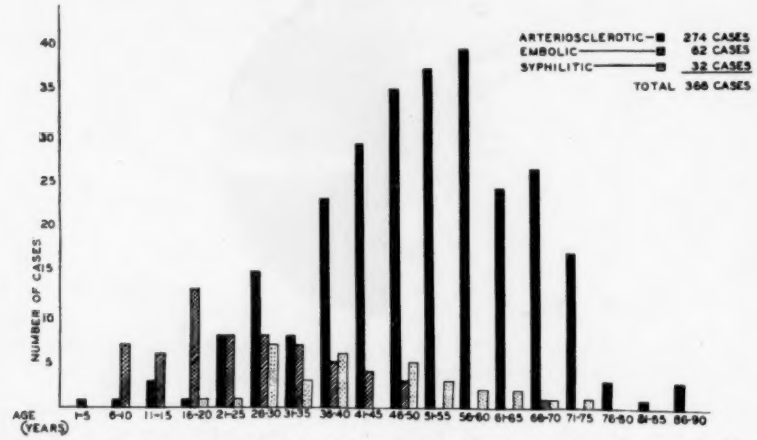

Chart 5.—Nature of pathologic lesions in the blood vessels, with age incidence, in 368 cases of intracranial aneurysms.

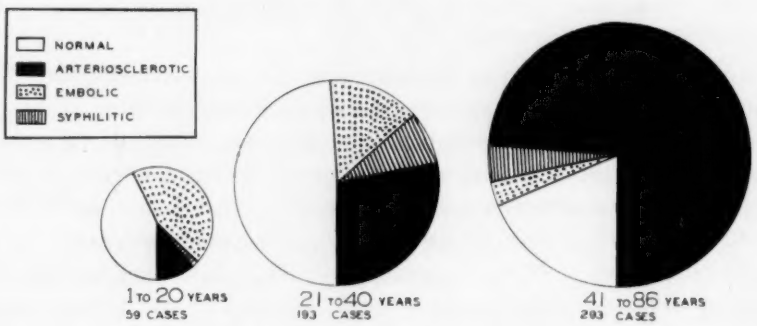

Chart 6.—Age distribution and pathologic lesions in 545 cases of intracranial aneurysms.

Of 59 patients aged 20 years or younger, 44 per cent had mycotic emboli and 44 per cent had normal arteries. Of 193 patients from 21 to 40 years of age, 49 per cent had normal vessels; 23 per cent had arteriosclerosis, and 15 per cent had mycotic emboli. Of 293 patients over 40 years of age, 74 per cent had arteriosclerosis, and 20 per cent had normal arteries.

REPORT OF CASES

We add to the literature the report of 2 cases which illustrate points of special interest.

CASE 1.—*Anomaly of the circle of Willis.*

History.—L. J., aged 24, fell unconscious while dancing and was taken to the Rhode Island Hospital on June 25, 1937. There was a suspicion of foul play. One hour later he was drowsy and vomited. The pulse rate was 50, the temperature 97 F., the respiratory rate 18 and the blood pressure 160 systolic and 115 diastolic. The neck was stiff. The spinal fluid was bloody and was under a pressure of 500 mm. of water. The left pupil was large and failed to react to light; the size and reaction of the right pupil were normal. The abdominal and cremasteric reflexes were absent. A Babinski sign was present on each side. The house officer on the neurologic service suggested the presence of a ruptured intracranial aneurysm. The surgeon did a subtemporal decompression to reduce the increased spinal fluid pressure. At this operation no subdural hematoma was seen. The patient died on the same day.

Necropsy.—Dr. Charles Ashworth, medical examiner, observed subarachnoid hemorrhage and atheromatous degeneration of the internal carotid arteries, the circle of Willis, the vertebral arteries and the basilar artery. There was marked tortuosity of these arteries, though the patient was only 24. There was a large ruptured aneurysm, 10 mm. in diameter, at the anterior end of the basilar artery, projecting toward the left. At this point there was a developmental anomaly. On the left side the basilar artery ended blindly in the aneurysm; it did not join the left posterior communicating artery to complete the circle of Willis and form the posterior cerebral artery. The left posterior cerebral artery was missing, and the circle of Willis was not completed. The posterior communicating artery on the side of the anomaly was greatly enlarged and supplied the field of the posterior cerebral artery without a branch from the basilar artery. (Normally the posterior communicating artery from the internal carotid and a branch from the basilar artery join to form the posterior cerebral artery and to complete the circle of Willis.)

Section of the brain showed an old area of softening of the right internal capsule and fresh hemorrhage in the posterior limb of the left internal capsule. There were syphilitic aortitis and a calcified polycystic kidney.

Additional History.—Subsequent to the death of the patient additional data were obtained of an acute upset when he was 17 years of age. At that time he had headache and weakness of the left leg, which lasted nine months. The blood pressure was 160 systolic and 120 diastolic. On the left side there were an exaggerated knee jerk and ankle jerk, ankle clonus and a positive Babinski sign. The spinal fluid was clear, with normal pressure, cell count and chemical constituents. Wassermann reactions of the blood and spinal fluid were negative.

Comment.—The patient was only 24. At the age of 17 he had had left hemiplegia and possibly an area of softening in the right internal capsule. In his last sickness he had signs of a subarachnoid hemorrhage. Necropsy showed a ruptured aneurysm of the basilar artery, extensive atheromatous degeneration of the cerebral arteries, an anomaly of the circle of Willis, syphilitic aortitis and a polycystic kidney.

In cases of intracranial aneurysm two types of developmental defects are sometimes seen. An aneurysm may be located at the site of a developmental defect of the muscular layer of the arterial wall, as described by Forbus. Or, as in the case cited, there may be a gross anomaly of the circle of Willis. As we have pointed out, there was no branch from the basilar artery on the left side to meet the posterior cerebral artery and complete the circle of Willis. In the embryo anterior, middle and posterior branches grow from the internal carotid artery. Later, a branch from the basilar artery grows up to join the posterior branch of the carotid artery. In this case the link between the basilar and the posterior branch of the carotid artery was missing.

CASE 2.—*Palsy of the third nerve.*

History—J. A., a white man aged 42, was admitted to the neurologic service of the Rhode Island Hospital on Feb. 25, 1937. Six days before, while working as a tool maker, he had been suddenly overcome by a violent headache and pain in the back of the neck. On the morning before admission he had a "spell," in which he stiffened and lost consciousness. On admission the pulse rate was 80, the temperature 98 F., the respiratory rate 20 and the blood pressure 100 systolic and 70 diastolic. His mind was clear. There were stiffness of the neck, a Kernig sign bilaterally and a Babinski sign on the right. The spinal fluid was bloody and under a pressure of 190 mm. of water. Wassermann reactions of the blood and spinal fluid were negative. For fifteen days after admission he showed gradual improvement. On waking in the morning of the sixteenth day he complained of diplopia and showed complete palsy of the right third cranial nerve. The spinal fluid was again bloody. On the twenty-seventh day the spinal fluid contained 1,500 red cells per cubic millimeter, and on the thirty-fifth day, 14 red cells. Palsy of the third nerve continued. On the thirty-sixth day the neck sign reappeared. There were hyperactive deep reflexes, with Kernig and Babinski signs bilaterally. Ptosis, external strabismus and enlargement of the pupil of the right eye was present. The spinal fluid had 2,250 red cells per cubic millimeter. He became stuporous on the forty-eighth day and died on the fifty-fourth day.

Autopsy.—Dr. Robert Williams found fresh blood in the subarachnoid space and a small ruptured aneurysm of the right internal carotid artery, between the origin of the posterior communicating and that of the anterior choroid artery. In contact with this ruptured aneurysm was a round blood clot, about 8 mm. in diameter, which was covered by a glistening membrane. The right third cranial nerve was flattened like a fan over the medial surface of the blood clot. The arteries of the circle of Willis showed no anomaly, no atheroma and no pathologic change other than the aneurysm. Section of the brain showed no tumor or hemorrhage, but there was an area of softening in the anterior part of the left caudate nucleus.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms

No.	Arteries Involved*	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
1	P. Comm. (both)	60	M	—	Vessels rigid, with deposit on inner lining	Morgagni: De sedibus et causis morborum, Venetiis, ex. typog. Remondiniana, 1761, book 1, letter 4, case 19
2	I. C.	52	F.	+	Not stated	Blumi, in Sandifort: Thesaurus dissertationum, Lugd. Bat., S. et J. Luchtmans [and others], 1778, vol. 3, p. 373
3	I. C. (both)	64	F	—	Not stated	Blane: Tr. Soc. Improve. M. & Chir. Knowl. **2**: 193, 1797
4	Bas.	20	F	+	Not stated	Blackall: Observations on the Nature and Cure of Dropsies, ed. 2, London, Longman [and others], 1814; ed. 4, Philadelphia, J. Webster, 1820, p. 169
5	Bas.	20	F	+	Not stated	Hodgson: A Treatise on the Diseases of Arteries and Veins, London, T. Underwood, 1815, pp. 76 and 132-133
6	A. C.	57	M	+	Calcareous deposits on coats of vessels	Ibid.
7	A. C.	Young	M	+	Not stated	Ibid.
8	R. A. C.	57	M	+	Coats of aneurysm thick	Spurgin: London M. Reposit. **23**: 443, 1825
9	Bas.	59	M	+	Middle layer of sac cartilaginous	Serres: Arch. gén. de méd. **10**: 419 and 421, 1826
10	A. Comm.	50	F	+	Not stated	Ibid.
11	R. M. C.	..	M	..	Not stated	Lancet **11**: 157, 1826-1827
12	L. M. C.	19	M	+	Not stated	Bright, R.: M. Rep. **2**: 266 and 267, 1827; **3**: 614, 1827
13	L. M. C.	45	M	+	Not stated	Ibid.
14	L. P. Comm.	39	F	+	Not stated	Chevalier: London M. & Phys. J. **58**: 498, 1827
15	Bas.	35	M	—	Carotid and vertebral arteries normal	Bright, J.: Lancet **2**: 727, 1828-1829
16	Bas.	..	..	+	Coats of vessels cartilaginous	Bouillaud: Med.-Chir. Rev. **10**: 585, 1829
17	Bas.	21	F	+	Calcareous deposits on vessels	Ibid.
18	L. Vert.	24	M	+	Arteries diseased, in some places cartilaginous	Farre: Med.-Chir. Rev. **10**: 211, 1829
19	L. M. C.	65	F	+	No bone or other appearance of disease	"Delta": Med.-Chir. Rev. **14**: 234, 1831
20	R. M. C.	60	M	+	Walls thin but firm	Mussy: Arch. gén. de méd. **26**: 559, 1831
21	R. M. C.	60	M	+	Sac with thin, firm parietes	Flandin: Bull. Soc. anat. de Paris **7**: 26, 1832
22	Bas.	54	M	+	.....	Jennings: Lancet **2**: 397, 1832-1833
23	R. I. C.	42	F	+	.....	Stilling: Ztschr. f. Ophth. **3**: 465, 1833
24	L. I. C.	..	..	—	.....	Breschet: Mémoires chirurgicaux sur différentes espèces d'anévrysmes, Paris, J.-B. Baillière, 1834, p. 25, table 5
25	L. A. C.	28	F	—	Middle layer thick	Nebel: Observatio duorum aneurysmatum rariorum, quorum alterum ex arcu aortae, alterum ex arteria corporis callosi ortum est, Inaug. Dissert., Heidelberg, G. Reichard, 1834
26	R. Vert.	..	..	—	.....	Cruveilhier: Anatomie pathologique du corps humain, Paris, J.-B. Baillière, 1835, vol. 2, no. 28, plate 3
27	Bas.	68	M	—	Yellow plaques on surface	Lebert: Bull. Soc. anat. de Paris **11**: 22, 1836
28	I. C.	60	M	+	.....	Albers: Gaz. méd. de Paris **5**: 714, 1837

In this table, A. C. indicates the anterior cerebral artery; A. Comm., the anterior communicating artery; A. Inf. Cereb., the anterior inferior cerebellar artery; A. Perf., the anterior perforating artery; Bas., the basilar artery; I. C., the internal carotid artery; Inf. Cereb., the inferior cerebellar artery; M. C., the middle cerebral artery; M. F., the middle fossa; Ophth., the ophthalmic artery; P. C., the posterior cerebral artery; P. Comm., the posterior communicating artery; P. Inf. Cereb., the posterior inferior cerebellar artery; S. Cereb., the superior cerebellar artery; Vert., the vertebral artery; L., left, and R., right.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
29	Bas.	20	F	—	.....	Ollivier: De la moëlle épinière, et de ses maladies, Paris, Meguigon-Marvis & fils, 1837, vol. 1, p. 452
30	Bas.	59	M	+	Middle layer of artery cartilaginous	Ibid.
31	R. M. C.	35	M	+	Other vessels normal	Burne: London M. Gaz. **1**: 453, 1838-1839
32	P. C.	20	F	—	.....	Delpech: Bull. Soc. anat. de Paris **17**: 112, 1842
33	Bas.	14	M	—	Middle layer of wall thickened	Kingston: Edinburgh M. & S. J. **57**: 69, 1842
34	L. I. C.	49	M	+	Vessels thickened	Thomson: London & Edinburgh Month. J. M. Sc. **2**: 568, 1842
35	Bas.	41	M	+	Arteries atheromatous	Pfeufer: Ztschr. f. rat. Med. **1**: 293, 1844
36	Bas.	54	M	—	.....	Smith: Dublin M. J. **25**: 507, 1844
37	Bas.	58	M	+	.....	Eager: London M. Gaz. **3**: 384, 1846
38	R. P. Comm.	20	F	+	.....	France: Guy's Hosp. Rep. **4**: 46, 1846
39	L. P. Comm. at I. C.	62	F	+	.....	Francis: London M. Gaz. **3**: 213, 1846
40	Bas.	58	M	+	.....	Lager: Arch. gén. de méd. **12**: 482, 1846
41	Bas.	47	M	+	.....	Ruschenberger: Am. J. M. Sc. **11**: 64, 1846
42	L. P. C.	34	M	+	.....	Carson: Edinburgh M. & S. J. **68**: 103, 1847
43	L. I. C.	35	M	+	.....	Corfe: London M. Times **16**: 590, 1847
44	Bas.	..	M	—	.....	Ibid.
45	L. I. C.	52	F	+	Arteries healthy	Moore: Tr. Path. Soc. London **1**: 242, 1847-1848
46	Bas.	33	M	+	.....	Bowen: New York J. Med. **3**: 345, 1849
47	I. C.	39	F	+	No calcareous deposit in cerebral vessels	Douglas: London J. Med. **1**: 301, 1849
48	Bas.	35	M	+	Other arteries healthy	Gordon: London M. Times **19**: 381, 1849
49	Vert.	..	M	—	Calcareous deposit in wall of sac	Neill: Am. J. M. Sc. **18**: 122, 1849
50	L. P. Comm.	18	F	+	No fatty atheromatous changes in carotid or basilar arteries	Hare: Tr. Path. Soc. London **2**: 169, 1849-1850
51	L. I. C.	70	F	—	.....	Barth: Bull. Soc. anat. de Paris **24**: 348, 1850
52	Bas.	30	M	+	Other vessels without changes	Hardy: Gaz. d. hôp. **23**: 170, 1850
53	L. M. C.	35	M	+	.....	Fletcher: Prov. M. & S. J., 1851, p. 72
54	Bas.	38	M	—	.....	Andrew, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
55	I. C.	65	M	—	.....	Hewett, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
56	Bas.	..	M	—	.....	Lakin, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
57	M. C.	..	F	+	.....	Mackenzie, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
58	A. C.	21	F	—	.....	Roe, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
59	Bas.	45	M	—	.....	Ibid.
60	P. C.	20	F	—	.....	Shaw, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
61	Bas.	..	M	—	.....	Todd, cited by Brinton: Tr. Path. Soc. London **3**: 49, 1851-1852
62	Bas.	70	F	—	.....	Laboulbene-Lebert: Virchows Arch. f. path. Anat. **2**: 35, 1855
63	L. M. C.	..	M	+	Arteries not atheromatous	Ogle: Tr. Path. Soc. London **7**: 127, 1855-1856
64	R. M. C.	57	M	—	Vessels very atheromatous	Squire: Tr. Path. Soc. London **7**: 125, 1855-1856

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
65	Bas.	53	F	+	.....	van der Byl: Tr. Path. Soc. London **7**: 123 and 129, 1855-1856
66	R. P. C.	56	M	+	.....	Ibid.
67	Bas.	35	M	—	.....	Uhde: Deutsche Klin. **41**: 424, 1856
68	L. P. C.	40	F	—	Vessels thin but healthy	Squire: Tr. Path. Soc. London **8**: 166, 1856-1857
69	R. I. C. and R. Ophth.	52	F	+	Middle coat thickened	Giraudet: Gaz. d. hôp. **40**: 105, 1857
70	Bas.	54	M	—	Vertebral arteries thickened	Brunnische: Schmidt's Jahrb. **98**: 154, 1858
71	R. S. Cereb.	56	M	—	Atheromatous vessels	Bristowe: Tr. Path. Soc. London **10**: 3 and 4, 1858-1859
72	A. Comm.	60	F	+	Vessels thickened and rigid	Ibid.
73	L. I. C.	47	F	+	.....	Patterson: Edinburgh M. J. **4**: 722, 1858-1859
74	Bas.	34	M	+	Healthy vessels	Gull: Guy's Hosp. Rep. **3**: 281, 1859
75	L. M. C.	17	F	+	Embolic	Ibid.
76	L. A. C.	35	F	+	Healthy vessels	Ibid.
77	Bas.	43	F	+	Atheromatous changes	Ibid.
78	L. M. C.	30	F	+	.....	Ibid.
79	L. M. C.	58	M	+	Atheroma	Ibid.
80	Bas.	47	F	—	Plates in coats of aneurysm	Gueniot: Bull. Soc. anat. de Paris **35**: 321, 1860
81	Bas.	24	F	+	Embolic (endocarditis)	Oppolzer: Wien. med. Wchnschr. **10**: 132, 1860
82	L. I. C.	16	M	—	.....	Holmes: Tr. Path. Soc. London **12**: 61, 1860-1861
83	R. M. C.	24	M	+	Walls of sac calcareous	Murchison: Tr. Path. Soc. London **13**: 2, 1861-1862
84	Bas.	42	M	+	Vessels otherwise healthy	Blachez: Bull. Soc. anat. de Paris **37**: 335, 1862
85	Bas.	48	F	—	.....	Greisinger: Arch. d. Heilk. **3**: 550 and 553, 1862
86	Bas.	56	M	—	Atheromatous	Ibid.
87	L. M. C.	68	M	+	Wall of sac hard and cretaceous	Callender: Tr. Path. Soc. London **14**: 64, 1862-1863
88	L. M. C.	14	M	+	Walls of sack thick and atheromatous no disease of other vessels	Haldane: Edinburgh J. M. Sc. **8**: 189, 1862-1863
89	A. Comm.	60	F	—	Nearby vessels healthy	Struthers: Edinburgh J. M. Sc. **8**: 190, 1862-1863
90	Inf. Cereb.	..	..	..	Atheroma of other vessels	Fernet: Bull. Soc. anat. de Paris **39**: 495, 1864
91	Bas.	28	M	+	Healthy arteries	Russell: M. Times & Gaz. **1**: 493, 1864
92	Bas.	37	M	+	Other vessels slightly atheromatous	Fuller: Tr. Path. Soc. London **16**: 83, 1864-1865
93	L. I. C.	43	F	+	Walls atheromatous	Gougenheim: Bull. Soc. anat. de Paris **40**: 48, 1865
94	L. A. Cereb.	46	F	—	Vessels very atheromatous	Ogle: Brit. & For. Med.-Chir. Rev. **36**: 491, 1865
95	L. M. C.	53	M	+	Walls not atheromatous	Ibid.
96	L. I. C.	16	M	—	Vessels healthy	Ibid.
97	Bas.	39	M	+	No atheroma	Ibid.
98	L. A. C.	..	M	+	.....	Ibid.
99	Bas.	51	F	+	Arteries not diseased	Varrentrap: Arch. d. Heilk. **6**: 85, 1865
100	L. M. C.	24	M	+	Soft arteries	Wagner: Arch. d. Heilk. **5**: 285, 1865
101	A. Comm.	49	F	+	Other arteries healthy	Watson: London M. Times & Gaz **1**: 357, 1865
102	R. M. C.	59	F	+	.....	Broadbent: Tr. Path. Soc. London **17**: 57, 1865-1866
103	L. M. C.	21	F	+	No disease of vessels	Hayem: Compt. rend. Soc. de biol. **3**: 85, 1866
104	L. Vert.	61	F	+	.....	Sydow: Schmidt's Jahrb. **130**: 161, 1866
105	Bas.	61	F	+	Vessels atheromatous	Bouchard: Etude sur quelques points, de la pathogénie des hémorrhagiescérébrales, Thesis, Paris, no. 328, 1866; translated by T. J. Maclagan, London, Simpkin, Marshall & Co., 1872, p. 46

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
106	R. M. C.	78	F	+	No atheroma	Lépine: Gaz. méd. de Paris **22**: 701, 1867
107	L. I. C.	27	F	+	Arteries thickened	Bristowe: Tr. Path. Soc. London **19**: 174, 1867-1868
108	L. M. C.	29	F	+	.....	Wood: Tr. Path. Soc. London **19**: 102, 1867-1868
109	L. P. Comm.	53	F	+	Slightly atheromatous	Bourneville: Bull. Soc. anat. de Paris **43**: 449, 1868
110	L. M. C.	34	F	—	Walls of aneurysm atheromatous; vessels at base not diseased	Durand: Des anévrysmes du cerveau, Thesis, Paris, no. 251, 1868, pp. 14, 20, 29, 32 and 46
111	L. M. C.	86	M	—	Vessels very atheromatous	Ibid.
112	R. M. C.	60	F	+	Vessels very atheromatous	Ibid.
113	R. M. C.	56	F	—	Arteries sclerotic, with atheromatous plates	Ibid.
114	Bas.	59	F	+	Atheromatous changes	Ibid.
115	L. A. C.	49	M	+	Small atheromatous patches on wall	Lorber: Arch. gén. de méd. **11**: 229, 1868
116	L. I. C.	24	F	+	.....	Peacock: Lancet **2**: 542, 1868
117	L. M. C.	50	F	—	Thick and opaque, but not materially diseased	Bastian: Tr. Path. Soc. London **20**: 126, 1868-1869
118	L. M. C.	40	M	+	Vessels normal	Church: Tr. Path. Soc. London **20**: 109 and 111, 1868-1869
119	R. M. C.	13	M	+	Rest of arteries healthy	Church: Tr. Path. Soc. London **20**: 109 and 111, 1868-1869
120	Bas.	36	F	+	Old endocarditis; questionable embolic origin	Semple: Tr. Path. Soc. London **20**: 112, 1868-1869
121	R. I. C.	56	M	+	Several patches of degeneration on basilar artery	Adams: Brit. M. J. **2**: 768, 1869
122	Bas.	61	F	—	Vessels atheromatous	Berger: Bull. Soc. anat. de Paris **44**: 188, 1869
123	L. M. C.	48	F	+	Atheromatous plates on wall of vessel	Cazades: Bull. Soc. anat. de Paris **44**: 492, 1869
124	L. T. C	14	M	+	Other vessels healthy	Hutchinson: Pennsylvania Hosp. Rep. **2**: 83, 1869
125	L. Vert.	19	M	+	.....	Lorne: Bull. Soc. anat. de Paris **44**: 455, 1869
126	L. M. C.	28	M	+	.....	Pepper: Am. J. M. Sc. **67**: 403, 1869
127	R. M. C.	41	F	+	.....	Richardson: Brit. M. J. **1**: 74, 1869
128	R. M. C.	13	M	+	Other vessels healthy; embolic origin of aneurysm	Church: St. Barth. Hosp. Rep. **6**: 99, 1870
129	R. M. C.	15	M	+	Embolic origin	Ibid.
130	R. M. C.	20	M	+	Embolic origin	Ibid.
131	L. A. C.	17	F	+	Vessels healthy	Ibid.
132	R. Vert.	67	M	+	Atheroma of coats	Echeverria: On Epilepsy, New York, W. Wood & Co., 1870, pp. 53, 72 and 124
133	R. M. C.	12	F	+	Embolic occlusion (endocarditis)	Ibid.
134	R. M. C.	26	F	+	"Syphilitic" lesions	Ibid.
135	Bas.	26	M	—	Remaining vessels healthy	Russell: Brit. M. J. **2**: 87, 1870
136	P. C.	35	M	—	.....	Smith: Dublin Quart. J. M. Sc. **50**: 455, 456, 1870
137	L. M. C.	26	F	—	Vessel plugged by yellow fibrin (vegetations on aortic valves)	Ibid.
138	L. M. C.	..	F	+	Arteries at base highly atheromatous	Dickinson: Tr. Path. Soc. London **23**: 1, 1871-1872
139	A. Comm.	54	M	+	Atheromatous	Gee: St. Barth. Hosp. Rep. **7**: 147, 1871
140	Bas.	37	M	+	Calcareous degeneration of coats of vessel	Bartholow: Am. J. M. Sc. **64**: 373, 1872
141	L. Vert.	60	M	+	Vessels diseased	Foot: Provincial J. **1**: 424, 1872
142	L. P. C.	50	F	+	Slight atheromatous patches	Hanot: Bull. Soc. anat. de Paris **47**: 257, 1872
143	Bas.	49	M	+	.....	Lange: Hospitalstid. **75**: 205, 1872

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
144	Bas.	29	M	—	Other arteries at base atheromatous	Loomis: M. Rec. **6**: 501, 18.2
145	L. Vert.	45	M	+	Slight atheromatous changes	Sevestre: Bull. Soc. anat. de Paris **47**: 415, 1872
146	A. Comm.	68	M	—	Walls thick; other vessels healthy	Ebstein: Deutsches Arch. f. klin. Med. **12**: 617, 1873
147	Small arachnoid artery	27	M	+	Perforated embolized wall of small arachnoid artery	Ponfick: Virchows Arch. f. path. Anat. **58**: 528, 1873
148	Small arachnoid artery	29	M	+	Embolic	Ibid.
149	R. M. C.	40	M	+	Embolic	Ibid.
150	R. P. Comm.	20	F	+	Embolic	Ibid.
151	Arachnoid artery	24	M	+	Embolic arachnoiditis	Ibid.
152	Bas.	..	M	—	Vessels thickened	von Steinmann: Deutsches Arch. f. klin. Med. **13**: 186, 1874
153	I. C.	24	M	—	.....	Holmes: Arch. Ophth. **4**: 393, 1875
154	R. I. C.	40	F	—	Walls of sac partly calcified	Hutchinson: Lancet **1**: 546, 1875
155	S. Cereb.	60	F	+	Intense atheroma of vessels	MacSwiney: Dublin J. M. Sc. **59**: 373, 1875
156	A. Comm.	69	F	—	Vessels atheromatous	McDowall: Lancet **2**: 202, 1875
157	I. C. (both)	46	M	—	Intimal arteriosclerosis	Meyer: Arch. f. Psychiat. **6**: 84, 1875
158	L. I. C.	33	M	—	Marked arteriosclerosis	Ibid.
159	L. I. C.	53	F	+	Walls thick and atheromatous	Ross: Canad. M. & S. J. **3**: 348, 1875
160	L. M. C.	45	M	+	Vessels normal	Samt: Berl. klin. Wchnschr. **12**: 542, 1875
161	L. Vert.	56	M	—	.....	Schultze: Virchows Arch. f. path. Anat. **65**: 385, 1875
162	R. M. C.	43	M	+	.....	Westphal: Arch. gén. de méd. **2**: 728, 1875
163	A. Comm.	45	M	+	Arteries slightly atheromatous	Greenfield: Tr. Path. Soc. London **27**: 2, 1875-1876
164	A. Comm.	41	M	+	Rest of arteries free of atheroma	Legg and Omerod: St. Barth. Hosp. Rep. **12**: 239, 1876
165	L. M. C.	34	M	+	.....	Peacock: St. Thomas's Hosp. Rep. **7**: 119, 1876
166	R. I. C.	63	F	+	.....	Ibid.
167	R. M. C.	34	F	+	.....	Ibid.
168	R. M. C.	50	F	+	Atheromatous vessels	Marchant: Bull. Soc. anat. de Paris **1**: 755, 1876
169	R. M. C.	40	F	+	Healthy vessels	Bell: Canad. M. & S. J. **5**: 56, 1877
170	Bas.	53	F	—	.....	Mackenzie: J. Ment. Sc. **23**: 81, 1877
171	R. M. C.	18	F	—	.....	Robertson: Edinburgh M. J. **22**: 894, 1877
172	R. M. C.	42	M	+	Arteries tortuous and small in caliber; deposits of calcareous degeneration	Wood: Brit. M. J. **2**: 589, 1877
173	L. I. C.	22	F	—	Vessels healthy, probably embolic	Greenfield: Tr. Path. Soc. London **29**: 94, 1877-1878
174	L. M. C.	40	M	+	Vessels at base healthy	Ibid.
175	Bas.	16	M	+	.....	Ibid.
176	A. Comm.	20	M	+	No other disease of vessels	Legg: Tr. Path. Soc. London **29**: 106, 1877-1878
177	R. M. C.	47	F	+	Very atheromatous	Macleod: J. Ment. Sc. **24**: 617, 1878
178	R. P. C.	12	M	+	Embolic (endocarditis)	Rauchfuss: Jahresb. ü. d. Fortschr. d. ges. Med. **13**: 102, 1878
179	L. M. C.	72	M	+	Vessels atheromatous	Russell: J. Ment. Sc. **24**: 614, 1878
180	R. A. C.	50	M	—	All arteries and aneurysm white and opaque; microscopic syphilitic changes of Heubner	Ibid.
181	L. I. C.	30	M	—	Thickening of vessels with syphilitic infiltration of small cells	Ibid.
182	Bas.	44	M	+	.....	Amidon: New York State J. Med. **31**: 193, 1880
183	L. M. C.	20	M	+	Not atheromatous	Osler: Montreal Gen. Hosp. Rep. **2**: 16, 1880
184	L. Vert.	36	M	+	Thickened walls; endarteritis	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
185	L. M. C.	55	..	—	Stiff and atheromatous	Ibid.
186	A. Comm.	40	F	+	Atheromatous spots	Ibid.
187	Bas.	75	F	—	Atheromatous	Reynier: Bull. Soc. anat. de Paris **5**: 167, 1880
188	R. M. C.	39	M	+	.....	Ridlon: M. Rec. **18**: 579, 1880
189	Bas.	57	M	+	Atheromatous vessels at base	Schmidt: Berl. klin. Wchnschr. **17**: 293, 1880
190	Bas.	44	M	+	.....	Biach: Wien. med. Wchnschr. **51**: 1421, 1881
191	R. I. C.	73	F	—	Very atheromatous	Féré: Bull. Soc. anat. de Paris **56**: 166, 1881
192	R. P. Comm.	80	F	—	Walls thickened	Klippel: Bull. Soc. anat. de Paris **56**: 539, 1881
193	A. Comm.	50	F	+	.....	Ord: Tr. Path. Soc. London **32**: 65, 1881-1882
194	L. P. Comm.	40	F	+	Healthy vessels	West: Tr. Path. Soc. London **32**: 66 and 69, 1881-1882
195	L. M. C.	12	M	+	Wall of sac atheromatous; other vessels healthy	West: Tr. Path. Soc. London **32**: 66 and 69, 1881-1882
196	Bas.	16	M	+	.....	Wright: Lancet **2**: 805, 1882
197	I. C.	..	F	+	.....	Glover: Lancet **1**: 539, 1883
198	Bas.	40	M	—	Atheromatous	Hallopeau and Giraudeau: Encéphale **3**: 657, 1883
199	A. Comm.	17	M	+	Healthy	Ross: M. News **42**: 251, 1883
200	.....	..	M	+	Embolic	Bastian: Tr. Clin. Soc. London **17**: 18, 1884
201	L. Vert.	61	M	—	Fatty degeneration of intima	Moser: Deutsches Arch. f. klin. Med. **35**: 438, 1884
202	L. M. C.	40	M	—	Calcareous clot in sac	Anderson: Lancet **2**: 852, 1885
203	L. M. C.	29	F	+	Atheroma	Loppe: Bull. Soc. anat. de Paris **60**: 24, 1885
204	L. I. C.	22	F	—	Walls hard; no atheromatous degeneration	Dempsey: Brit. M. J. **2**: 541, 1886
205	Bas.	27	M	+	"Syphilitic"	Spillman: Ann. de dermat. et syph. **7**: 641, 1886
206	L. I. C.	21	F	+	"Syphilis"	Ibid.
207	Bas.	36	M	+	No embolism or atheroma	Bramwell: Edinburgh M. J. **32**: 1, 1886; **32**: 911, 1887
208	R. M. C.	40	F	+	No embolism or atheroma	Ibid.
209	R. I. C.	31	M	—	.....	Ibid.
210	R. P. C.	43	F	—	Arteries free of atheroma	Ibid.
211	Small pial artery	49	F	+	Embolic (endocarditis)	Eppinger: Arch. f. klin. Chir. **35**: 205, 1887
212	R. Vert.	30	M	+	Embolic (endocarditis)	Ibid.
213	R. M. C.	30	M	+	Embolic (endocarditis)	Ibid.
214	L. Vert.	..	..	..	Arteriosclerosis	Oppenheim: Berl. klin. Wchnschr. **24**: 638, 1887
215	Vert.	..	..	..	Arteriosclerosis	Ibid.
216	Vert.	..	..	..	Arteriosclerosis	Ibid.
217	L. M. C.	20	F	—	Embolic	Pel: Ztschr. f. klin. Med. **12**: 327, 1887
218	L. M. C.	60	F	+	.....	Verco: Australas. M. Gaz. **7**: 6, 1887-1888
219	Bas.	53	F	+	.....	Watson: Lancet **2**: 718, 1888
220	Bas.	31	M	+	Aneurysm "congenital"	Biggs: Proc. New York Path. Soc., 1889, p. 107
221	Bas.	26	M	—	(Septic endocarditis)	Hutchinson: Tr. Ophth. Soc. U. Kingdom **9**: 152, 1889
222	A. Comm.	43	M	—	.....	Mitchell and Dercum: J. Nerv. & Ment. Dis. **16**: 44, 1889
223	A. Comm.	51	M	+	Arteries free of atheroma	Mott and Stedman: Lancet **2**: 15, 1889
224	A. C.	56	F	+	Arteriosclerosis	Thoma and Kaefer: Virchows Arch. f. path. Anat. **116**: 1, 1889
225	R. Vert.	6	M	+	? Septic embolus	Pitt: Brit. M. J. **1**: 827, 1890
226	L. M. C.	50	M	+	Septic embolus	Ibid.
227	R. M. C.	18	M	+	Septic embolus	Ibid.
228	R. M. C.	31	M	+	Septic embolus	Ibid.
229	R. M. C.	16	F	+	Septic embolus	Ibid.
230	R. I. C.	66	M	—	Atheromatous vessels	Ibid.
231	R. I. C.	56	M	—	Atheromatous vessels	Ibid.
232	L. I. C.	17	M	—	Septic embolus (endocarditis)	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
233	R. P. C.					
234	I. C. (both)					
235	R. M. C.					
236	R. M. C.					
237	R. M. C.					
238	R. M. C.	10-19 (5)		..	Septic embolus; endocarditis: 10 cases Atheromatous vessels: 1 case	Pitt: Brit. M. J. **1**: 827, 1890 (Pitt gives statistics for this group as a whole, but not for individual cases)
239	R. M. C.	20-29 (4)	M (8)			
240	R. M. C.	30-39 (2)	F (7)			
241	L. M. C.	40-49 (2)		..		
242	L. M. C.					
243	L. M. C.					
244	L. M. C.					
245	L. M. C.					
246	L. M. C.					
247	Bas.	60	F	—	Very atheromatous	Cattell: Tr. Path. Soc. Philadelphia **16**: 149, 1891-1893
248	Bas.	35	M	+	Other vessels healthy	Klippel and Boeteau: Bull. Soc. anat. de Paris **67**: 81, 1892
249	Bas.	7	M	+	.....	Oppe, cited by van Hoffmann: Wien. klin. Wchnschr. **7**: 823, 1894
250	L. M. C.	47	M	—	No atheroma	Jayle: Bull. Soc. anat. de Paris **68**: 241, 1893
251	R. I. C.	26	F	+	Soft arteries	Atlas: Allg. Wien. med. Ztg. **39**: 489, 1894
252	R. M. C.	46	M	+	.....	von Hoffman: Wien. klin. Wchnschr. **7**: 823, 1894
253	L. Vert.	10	F	+	.....	Ibid.
254	L. Vert.	14	M	+	.....	Ibid.
255	L. Vert.	43	M	+	.....	Ibid.
256	L. Vert.	55	M	+	.....	Ibid.
257	L. Vert.	72	F	+	.....	Ibid.
258	L. Vert.	60	F	+	.....	Ibid.
259	L. Vert.	49	F	+	.....	Ibid.
260	Bas.	40	F	+	.....	Ibid.
261	R. Vert.	41	M	+	.....	Ibid.
262	R. Vert.	73	F	+	.....	Ibid.
263	R. Vert.	73	F	+	.....	Ibid.
264	Bas.	43	M	+	.....	Ibid.
265	Bas.	42	M	+	.....	Ibid.
266	Bas.	32	M	+	.....	Ibid.
267	Bas.	55	M	+	.....	Ibid.
268	Bas.	25	M	+	.....	Ibid.
269	Bas.	32	M	+	.....	Ibid.
270	Bas.	61	F	+	.....	Ibid.
271	Bas.	46	F	+	.....	Ibid.
272	Bas.	79	F	+	.....	Ibid.
273	P. Comm.	49	F	+	.....	Ibid.
274	P. Comm.	36	F	+	.....	Ibid.
275	L. A. C.	36	M	+	.....	Ibid.
276	L. A. C.	60	F	+	.....	Ibid.
277	L. A. C.	63	F	+	.....	Ibid.
278	L. A. C.	60	F	+	.....	Ibid.
279	R. A. C.	57	F	+	.....	Ibid.
280	R. A. C.	Old	F	+	.....	Ibid.
281	.....	..	F	+	.....	Ibid.
282	R. Ophth.	67	F	+	.....	Ibid.
283	A. Comm.	28	M	+	.....	Ibid.
284	A. Comm.	63	F	+	.....	Ibid.
285	A. Comm.	40	M	+	.....	Ibid.
286	A. Comm.	31	M	+	.....	Ibid.
287	A. Comm.	73	F	+	.....	Ibid.
288	A. Comm.	53	F	+	.....	Ibid.
289	A. Comm.	57	F	+	.....	Ibid.
290	A. Comm.	45	F	+	.....	Ibid.
291	A. Comm.	44	F	+	.....	Ibid.
292	A. Comm.	64	F	+	.....	Ibid.
293	A. Comm.	62	F	+	.....	Ibid.
294	A. Comm.	54	F	+	.....	Ibid.
295	L. I. C.	45	M	+	.....	Ibid.
296	L. I. C.	65	F	+	.....	Ibid.
297	L. I. C.	64	F	+	.....	Ibid.
298	L. I. C.	69	F	+	.....	Ibid.
299	L. I. C.	42	F	+	.....	Ibid.
300	L. I. C.	67	F	+	.....	Ibid.
301	R. I. C.	55	F	+	.....	Ibid.
302	R. I. C.	72	F	+	.....	Ibid.
303	R. I. C.	48	F	+	.....	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
304	R. I. C.	43	F	+	.....	von Hoffman: Wien. klin. Wchnschr. **7**: 823, 1894
305	R. I. C.	70	F	+	.....	Ibid.
306	R. I. C.	48	F	+	.....	Ibid.
307	R. I. C.	61	M	+	.....	Ibid.
308	R. M. C.	54	M	+	.....	Ibid.
309	R. M. C.	43	F	+	.....	Ibid.
310	R. M. C.	51	F	+	.....	Ibid.
311	R. M. C.	56	F	+	.....	Ibid.
312	R. M. C.	50	F	+	.....	Ibid.
313	R. M. C.	30	F	+	.....	Ibid.
314	L. M. C.	28	F	+	.....	Ibid.
315	L. M. C.	43	M	+	.....	Ibid.
316	L. M. C.	42	M	+	.....	Ibid.
317	L. M. C.	50	M	+	.....	Ibid.
318	L. M. C.	56	F	+	.....	Ibid.
319	L. M. C.	53	F	+	.....	Ibid.
320	L. M. C.	73	F	+	.....	Ibid.
321	L. M. C.	45	F	+	.....	Ibid.
322	L. M. C.	32	F	+	.....	Ibid.
323	L. M. C.	52	F	+	.....	Ibid.
324	L. M. C.	60	F	+	.....	Ibid.
325	L. M. C.	29	F	+	.....	Ibid.
326	L. M. C.	81	F	+	.....	Ibid.
327	R. I. C.	26	M	+	.....	Ibid.
328	A. Comm.	36	M	+	.....	Ibid.
329	R. M. C.	46	M	+	.....	Ibid.
330	Bas.	29	M	+	.....	Bradford: Tr. Clin. Soc. London **28**: 1, 1895
331	L. I. C.	34	F	+	Wall of aneurysm had two patches of atheroma	White: Tr. Clin. Soc. London **28**: 5, 1895
332	R. I. C.	21	M	+	Other vessels healthy	Ibid.
333	L. M. C.	53	M	+	.....	Ashworth: Australas. M. Gaz. **16**: 442, 1897
334	Bas.	40	M	—	.....	Mamourski and Maloletkoff: Rev. neurol. **5**: 346, 1897
335	R. M. C.	47	F	+	.....	Ibid.
336	I. C.	69	F	—	.....	Ibid.
337	L. M. C.	50	F	+	.....	Stadelmann: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **2**: 597, 1897
338	Bas.	28	M	..	.....	Carr: Proc. New York Path. Soc., 1897-1898, p. 135
339	Bas.	54	M	—	.....	Coleman: Proc. New York Path. Soc., 1897-1898, p. 134
340	R. M. C.	70	F	+	Extensive sclerosis with atheromatous plaques	Adami: Montreal M. J. **27**: 597, 1898
341	Bas.	29	M	—	Syphilitic	Saquepee: Bull. Soc. anat. de Paris **74**: 714, 1899
342	L. Vert.	68	M	—	Vessels atheromatous	Ladame and von Monakow: Nouv. iconog. de la Salpêtrière **13**: 1, 1900
343	R. M. C.	76	F	+	.....	Laignel-Lavastine: Bull. Soc. anat. de Paris **76**: 165, 1901
344	Bas.	28	M	+	.....	Schultze: M. Rec. **59**: 434, 1901
345	R. M. C.	50	F	+	Atheroma	Shaw: J. Ment. Sc. **47**: 547, 1901
346	Small pial artery on right	11	F	+	Embolic (endocarditis)	Simmonds: Deutsche med. Wchnscr. **27**: 353, 1901
347	Pial artery, of L. hemisphere	10	M	+	Embolic (endocarditis)	Ibid.
348	R. M. C.	32	F	+	Embolic (endocarditis)	Ibid.
349	L. M. C.	27	F	+	Embolic (endocarditis)	Ibid.
350	R. P. Comm.	29	F	+	Normal vessels	Karplus: Arb. a. d. neurol. Inst. a. d. Wien. Univ., 1902, no. 8, p. 239
351	L. I. C.	45	F	+	Wall of left internal carotid artery thickened	Lindner: Wien. klin. Wchnschr. **15**: 1193, 1902
352	.....	34	M	+	"Syphilis"	Nothnagel: Wien. klin. Wchnschr. **15**: 992, 1902
353	R. P. Comm.	64	F	+	"Syphilis"	Roque and Leriche: Lyon méd. **101**: 908, 1903
354	R. I. C.	22	F	+	Healthy vessels	Waldo: Brit. M. J. **1**: 796, 1903
355	R. M. C.	39	F	+	Line of atheroma at point of aneurysm	Widal: Presse méd. **1**: 413, 1903

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
356	R. I. C.	40	F	+	.....	Beykovsky: Wien. med. Wchnschr. **54**: 823, 1904
357	A. Comm.	27	M	+	Walls of other arteries healthy	Bruce and Drummond: Rev. Neurol. & Psychiat. **2**: 737, 1904
358	Bas.	70	F	+	Atheroma	Froin: Les hémorragies sous-arachnoidiennes et le mécanisme de l'hématolyse en général, Thesis, Paris, no. 113, 1904, p. 70
359	I. C.	86	M	—	.....	Leri: Bull. Soc. anat. de Paris **79**: 343, 1904
360	R. I. C.	87	F	—	Atheroma	Marchand: Bull. Soc. anat. de Paris **79**: 263, 1904
361	R. A. C.	65	F	—	Atheroma of vessels	Rice: J. Ment. Sc. **50**: 305, 1904
362	R. Vert.	50	M	—	Localized syphilitic periarteritis of aneurysm	Hedinger: Cor-Bl. f. schweiz. Aerzte **35**: 261, 1905
363	R. P. Comm.	42	F	+	Marked sclerosis	Rindfleish: Deutsches Arch. f. klin. Med. **86**: 183, 1906
364	R. Vert.	51	F	+	.....	Ibid.
365	Bas.	40	M	—	"Syphilis"	Saathoff: Deutsches Arch. f. klin. Med. **84**: 384, 1905
366	Bas.	..	M	—	"Syphilis"	Ibid.
367	L. M. C.	6	F	+	Mycotic (staphylococcic endocarditis)	Fahr: München. med. Wchnschr. **53**: 96, 1906
368	Bas.	28	M	+	.....	Ohm: Deutsche med. Wchnschr. **2**: 1694, 1906
369	I. C.	..	..	+	.....	Ibid.
370	Vert. (both)	69	F	—	Arteriosclerosis	Ruston and Southard: Boston M. & S. J. **154**: 312, 1906
371	L. I. C.	..	..	—	.....	Beadles: Brain **30**: 285, 1907
372	M. C.	55	F	+	.....	Ibid.
373	L. M. C.	50	F	+	Arteries healthy	Ibid.
374	L. Vert. at P. Inf. Cereb.	65	F	—	Basilar artery tortuous and diseased	Ibid.
375	L. I. C.	84	F	—	.....	Ibid.
376	L. I. C.	48	F	—	No atheroma	Ibid.
377	Bas.	68	M	+	.....	Ibid.
378	A. C.	51	M	+	.....	Ibid.
379	A. Comm.	63	F	—	.....	Ibid.
380	L. I. C.	61	F	+	.....	Ibid.
381	R. I. C.	..	F	—	.....	Ibid.
382	Bas.	14	M	—	.....	Ibid.
383	L. M. C.	40	M	+	Vessels normal	Milani: Boll. d. Soc. Lancisiana d. osp. di Roma **27**: 122, 1907
384	L. A. C. at A. Comm.	28	M	+	Irregular, cartilaginous thickening of arteries at base	MacNalty: Lancet **2**: 1667, 1908
385	R. M. C.	65	M	—	Atheromatous vessels	Souques: Nouv. iconog. de la Salpêtrière **27**: 108, 1908
386	L. A. C.	30	M	+	Thickening: syphilitic endarteritis obliterans	Booth: J. Nerv. & Ment. Dis. **36**: 528, 1909
387	Vert.	57	M	—	.....	Longcope: Proc. Philadelphia Path. Soc. **31**: 13, 1909-1910
388	L. Vert.	..	F	—	Thick and hard	Boinet: Compt. rend. Soc. de biol. **69**: 210, 1910
389	R. M. C.	44	F	+	Arteriosclerosis	Pick: Berl. klin. Wchnschr. **47**: 383, 1910
390	L. M. C.	64	M	+	Arteriosclerosis	Ibid.
391	Bas.	27	M	+	Other arteries normal	Semon: Brit. M. J. **2**: 312, 1910
392	L. M. C.	53	M	—	"Syphilis"	Chalier and Nové-Josserand: Lyon méd. **117**: 596, 1911
393	R. I. C.	42	F	+	.....	Freud: Wien. klin. Wchnschr. **61**: 905, 1911
394	R. I. C.	37	M	—	.....	Kummell: München. med. Wchnschr. **58**: 1293, 1911
395	Bas.	..	M	+	Healthy vessels	Mathew and Pirie: Rev. Neurol. & Psychiat. **9**: 107, 1911
396	L. I. C.	62	F	+	.....	Posey: Ophth. Rec. **20**: 200, 1911
397	L. P. C.	36	F	—	Aneurysm "congenital"	Versé: München. med. Wchnschr. **58**: 544, 1911
398	R. A. Inf. Cereb.	25	F	+	Thickening of vessels	Wichern: München. med. Wchnschr. **58**: 2724, 1911
399	L. Vert.	42	M	+	Both cerebral arteries thickened	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
400	L. I. C.	55	M	—	.....	Cushing: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, pp. 96 and 99
401	.....	31	M	—	No arteriosclerosis	Ibid.
402	R. M. C.	63	F	+	Arteriosclerosis	Wichern: Deutsche Ztschr. f. Nervenh. **44**: 220 1912
403	R. M. C.	44	M	+	Arteriosclerosis	Ibid.
404	L. M. C.	37	M	+	Aneurysm "congenital"	Ibid.
405	L. P. Inf. Cereb.	56	F	+	Aneurysm "congenital"	Ibid.
406	L. M. C.	32	M	+	Aneurysm "congenital"	Ibid.
407	R. A. C.	21	F	+	Aneurysm "congenital"	Ibid.
408	R. Vert.	38	M	+	Aneurysm "congenital"	Ibid.
409	L. M. C.	40	F	+	Embolic (endocarditis)	Ibid.
410	R. M. C.	22	M	+	Embolic (endocarditis)	Ibid.
411	L. M. C.	42	M	+	Embolic (endocarditis)	Ibid.
412	R. P. C.	37	F	+	Embolic (endocarditis)	Ibid.
413	L. M. C.	48	F	+	Aneurysm "congenital"	Ibid.
414	R. M. C.	57	F	+	Arteries soft	Ibid.
415	L. P. Inf. Cereb.	36	F	+	Walls healthy (probably embolic)	Ibid.
416	L. I. C.	42	F	+	Aneurysm "congenital"	Ibid.
417	L. Vert.	42	M	+	Vessels somewhat thickened; "congenital" (?)	Ibid.
418	R. A. Inf. Cereb.	25	F	+	Aneurysm "congenital"	Ibid.
419	Bas.	56	F	+	Syphilitic endarteritis of cerebral arteries	Ibid.
420	L. A. C.	51	F	+	Syphilitic endarteritis obliterans of cerebral vessels	Ibid.
421	R. M. C.	52	M	+	Aneurysm "congenital" (?); scattered deposits on soft vessels	Ibid.
422	A. Comm.	38	F	+	Aneurysm "congenital"(?); healthy vessels	Ibid.
423	R. Vert.	31	F	—	"Syphilis"	Babonneix: Gaz. d. hôp. **86**: 1253, 1913
424	R. Vert.	37	M	—	Endarteritis	Bailey: M. Rec. **83**: 268, 1913
425	R. P. Inf. Vereb.	6	F	+	Atheroma	Haike and Lewy: Tr. Internat. Cong. Med. (Sect. 11, Neuropath.), 1913, pt. 2, p. 27
426	R. A. Inf. Cereb.	42	M	+	Soft vessels	Orth: München. med. Wchnschr. **60**: 1038, 1913
427	L. I. C.	41	M	—	.....	Reinhardt: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**: 432, 1913
428	R. P. Comm.	30	F	+	No arteriosclerosis	Ibid.
429	L. A. C.	40	F	+	Aneurysm congenital no syphilis or arteriosclerosis	Ibid.
430	R. M. C.	58	F	+	Only slight thickening	Ibid.
431	R. M. C.	72	M	+	Marked arteriosclerosis	Ibid.
432	R. M. C.	72	M	+	Arteriosclerosis	Ibid.
433	L. P. C.	18	M	+	Aneurysm congenital; no syphilis or arteriosclerosis	Ibid.
434	L. side	56	M	+	Small grayish white flecks on vessels	Ibid.
435	L. M. C.	42	F	+	Small sclerotic plaques	Ibid.
436	R. P. C.	36	M	+	Syphilis; gummatous arteritis	Ibid.
437	R. I. C.	..	F	+	Atheroma on all arteries	Roberts: Tr. Am. Laryng., Rhin. & Otol. Soc. **19**: 442, 1913

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
438	L. M. C.	12	M	+	.....	von Jagic and Reibmayer: Wien. med. Wchnschr. **53**: 2563, 1913
439	.....	33	M	+	.....	Ibid.
440	Bas.	57	M	—	.....	Rhein: J. Nerv. & Ment. Dis. **41**: 360, 1914
441	L. A. C. at A. Comm.	50	M	+	Embolism (endocarditis)	Lowy: Zentralbl. f. inn. Med. **36**: 469, 1915
442	R. Vert.	40	F	+	Proliferative endarteritis	Weidman: J. A. M. A. **65**: 1105, 1915
443	L. P. Inf. Cereb.	..	M	+	.....	Woods: U. S. Nav. M. Bull. **9**: 434, 1915
444	Bas.	53	M	—	Arteriosclerosis	Semerak: Tr. Chicago Path. Soc. **10**: 128, 1916-1917
445	R. M. C.	7	F	+	Embolic	Fearnsides: Brain **39**: 224, 1916
446	R. A. C.	41	M	+	Embolic	Ibid.
447	L. M. C.	16	M	+	Embolic	Ibid.
448	R. M. C.	22	M	—	Embolic	Ibid.
449	L. Ant. Perf.	..	M	+	Embolic	Ibid.
450	L. A. C.	..	..	—	Embolic	Ibid.
451	R. M. C.	31	M	+	Embolic	Ibid.
452	R. M. C.	16	F	+	Embolic	Ibid.
453	L. I. C.	15	F	—	Embolic	Ibid.
454	R. M. C.	..	M	+	Embolic	Ibid.
455	Bas.	..	..	—	Embolic	Ibid.
456	L. M. C.	36	M	+	Embolic	Ibid.
457	.....	..	..	—	Embolic	Ibid.
458	L. M. C.	67	F	+	Atheroma	Ibid.
459	R. M. C.	60	F	+	.....	Ibid.
460	L. A. C. at A. Comm.	53	M	+	Arteriosclerosis	Ibid.
461	R. M. C.	48	F	—	.....	Ibid.
462	R. I. C.	47	M	—	.....	Ibid.
463	L. M. C.	..	..	—	.....	Ibid.
464	L. P. Inf. Cereb. at Bas.	42	F	+	No atheroma	Ibid.
465	R. A. C. at A. Comm.	41	M	..	No atheroma	Ibid.
466	R. P. Comm. at R. P. C.	40	F	+	.....	Ibid.
467	L. I. C.	36	M	+	Atheroma	Ibid.
468	L. I. C. at L. P. Comm.	36	F	+	Slight arterial degeneration	Ibid.
469	L. I. C.	28	M	+	"Congenital" aneurysm	Ibid.
470	R. M. C.	22	M	+	"Congenital" aneurysm	Ibid.
471	L. A. Cereb.	22	M	+	"Congenital" aneurysm	Ibid.
472	L. I. C. at L. P. Comm.	19	M	+	Arteries healthy	Ibid.
473	R. I. C.	40	M	+	Vessels healthy	Ibid.
474	R. M. C.	51	M	+	Atheroma	Ibid.
475	R. M. C.	48	F	+	Arterial degeneration	Ibid.
476	R. M. C.	60	M	+	Atheroma	Ibid.
477	L. A. C. at A. Comm.	49	F	+	Atheroma	Ibid.
478	L. A. C. at A. Comm.	49	M	+	Atheroma	Ibid.
479	L. A. C. at A. Comm.	44	F	+	Atheroma	Ibid.
480	R. M. C.	86	M	—	Atheroma of most of cerebral arteries	Ibid.
481	.....	75	M	—	.....	Ibid.
482	R. A. C. at A. Comm.	50	M	+	.....	Ibid.
483	R. A. C. at A. Comm.	55	M	+	.....	Ibid.
484	R. M. C.	53	M	—	.....	Ibid.
485	R. A. C. at A. Comm.	46	F	+	Arterial degeneration	Ibid.
486	L. A. C. at A. Comm.	72	F	+	Arterial degeneration	Ibid.
487	L. I. C.	70	F	—	.....	Freund: Klin. Monatsbl. f. Augenh. **56**: 468, 1916
488	L. M. C.	53	F	+	Arteriosclerosis	Ingvar: Nouv. iconog. d. Salpétrière **28**: 313, 1916-1918
489	R. M. C.	37	F	+	Other vessels normal	Ibid.
490	R. I. C.	53	F	+	"Congenital" origin	Kennedy: J. A. M. A. **67**: 1361, 1916

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
491	I. C.	32	F	+	.....	Doubler and Marlow: Arch. Ophth. **46**: 533, 1917
492	L. Vert.	47	M	+	Vessels soft	Hedinger: Cor.-Bl. f. schweiz. Aerzte **47**: 1395, 1917
493	R. I. C.	52	F	+	.....	Shannon: Arch. Ophth. **46**: 518, 1917
494	R. A. C.	12	F	+	Vessels healthy	Travers: West London M. J. **22**: 89, 1917
495	R. M. C.	21	M	+	.....	Elsberg: Neurol. Bull. **1**: 210, 1918
496	L. P. C.	54	M	+	.....	McMullin: U. S. Nav. M. Bull. **12**: 702, 1918
497	R. I. C.	26	F	+	.....	Viets: J. Nerv. & Ment. Dis. **47**: 249, 1918 (death of patient reported by Cushing: Guy's Hosp. Rep. **73**: 159, 1923)
498	R. M. C.	35	M	+	Arteriosclerosis	Kerpola: Arb. a. d. path. Inst. d. Univ. Helsingfors **2**: 115, 1919
499	L. M. C.	45	M	+	Arteriosclerosis	Ibid.
500	R. P. Comm.	56	M	+	Scattered plaques	Ibid.
501	R. Vert.	28	M	+	Slight intimal thickening of other vessels	Ibid.
502	L. M. C.	42	M	+	Arteriosclerosis	Ibid.
503	R. P. Comm.	36	F	+	Vessels soft	Ibid.
504	Bas.	53	M	+	Arteriosclerosis	Ibid.
505	Bas.	55	M	+	Vessels thickened with plaques	Ibid.
506	L. M. C. at P. Comm.	53	M	+	Scattered patches of intimal thickening	Ibid.
507	L. A. C. at A. Comm.	39	F	+	Scattered patches of intimal thickening	Ibid.
508	L. A. C. at A. Comm.	68	F	+	Marked thickening of vessels	Ibid.
509	R. M. C.	..	..	+	Scattered thickening	Ibid.
510	A. Comm.	..	..	+	Scattered yellow patches on intima	Ibid.
511	L. M. C.	1½	M	+	Focal areas of intimal thickening	Talbot, in Contributions to Medical and Biological Research, Dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919, vol. 2, p. 1004
512	M. C.	18	M	+	Vessels soft and thin	von Hansemann: Med. Klin. **15**: 57, 1919
513	M. C.	27	M	+	No trace of syphilis or arteriosclerosis; microscopically a decrease in elastic fibers in media of vessels	Ibid.
514	Bas.	36	M	—	.....	Leroy: Arch. méd. belges **73**: 139, 1920
515	A. Comm.	67	F	+	.....	Busse: Virchows Arch. f. path. Anat. **229**: 178, 1920
516	A. Comm.	55	M	+	Sclerosis of cerebral arteries	Ibid.
517	R. A. C. at A. Comm.	56	F	+	.....	Ibid.
518	A. Comm.	37	F	+	.....	Ibid.
519	A. Comm.	50	F	+	.....	Ibid.
520	A. Comm.	29	F	+	.....	Ibid.
521	A. Comm.	28	M	+	.....	Ibid.
522	L. P. C.	9	M	+	Infected embolus; other vessels normal	Drennan: New Zealand M. J. **20**: 324, 1921
523	L. A. C.	44	M	+	Infected embolus; slight intimal thickening of other vessels	Ibid.
524	L. A. C. at A. Comm.	52	F	+	Atheroma	Ibid.
525	A. Comm.	61	F	+	Atheroma	Ibid.
526	L. A. C. at A. Comm.	57	F	+	Atheroma	Ibid.
527	L. A. C. at A. Comm.	46	M	—	Atheroma	Ibid.
528	A. Comm.	46	F	+	Atheroma	Ibid.
529	A. Comm.	27	F	+	Atheroma (slight)	Ibid.
530	L. A. C. at A. Comm.	37	M	+	Medial sclerosis and intimal thickening	Ibid.
531	L. A. C. at A. Comm.	44	M	+	Other vessels normal	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
532	.....	20	M	+	.....	Foerster: Berl. klin. Wchnschr. **58**: 1057, 1921
533	R. Vert.	50	M	—	.....	Morrow: M. Rec. **100**: 894, 1921
534	A. C. at A. Comm.	18	M	+	.....	Pedersen: Hospitalstid. **64**: 721, 1921
535	Vert.	61	..	—	.....	Ibid.
536	.....	39	..	+	Arteriosclerosis	Ibid.
537	R. I. C.	50	F	+	Arteriosclerosis	Bachstez: Ztschr. f. Augenh. **49**: 349, 1922
538	Bas.	36	M	—	.....	Krabbe and Backer: Acta med. Scandinav. **56**: 95, 1922
539	A. Comm.	39	M	+	Embolism (endocarditis)	Lowy: Zentralbl. f. inn. Med. **43**: 505, 1922
540	I. C.	Young	F	..	.....	Nordeau and Moreau: Loire méd. **36**: 377, 1922
541	R. M. C.	13	M	+	(Coarctation of aorta)	Strassmann: Beitr. z. gerichtl. Med. **5**: 91, 1922
542	Bas.	46	M	—	.....	Wade: J. Roy. Army M. Corps **39**: 216, 1922
543	L. Vert.	54	M	—	Arteriosclerosis with calcification	Wells: Arch. Neurol. & Psychiat. **7**: 311, 1922
544	L. M. C.	33	M	+	Mycotic embolism	Berger: Virchows Arch. f. path. Anat. **245**: 138, 1923
545	L. M. C.	16	F	+	Mycotic embolism	Ibid.
546	R. I. C.	57	..	—	Arteriosclerosis	Ibid.
547	L. A. C. at A. Comm.	74	M	—	Arteriosclerosis	Ibid.
548	L. M. C.	70	F	+	Arteriosclerosis	Ibid.
549	L. I. C.	60	F	+	Arteriosclerosis	Ibid.
550	L. P. C.	64	F	+	Arteriosclerosis	Ibid.
551	L. M. C. at P. Comm.	69	F	+	Arteriosclerosis	Ibid.
552	A. Comm.	64	F	—	Arteriosclerosis	Ibid.
553	R. P. C.	70	F	+	Arteriosclerosis	Ibid.
554	M. C. (both)	70	F	—	Arteriosclerosis	Ibid.
555	R. I. C.	61	F	+	Arteriosclerosis	Ibid.
556	R. M. C.	56	F	+	Arteriosclerosis	Ibid.
557	A. Comm.	52	F	+	Arteriosclerosis	Ibid.
558	L. I. C.	57	F	—	Syphilis and arteriosclerosis	Ibid.
559	L. I. C.	50	F	—	Arteriosclerosis	Ibid.
560	L. A. C. at A. Comm.	49	M	+	.....	Ibid.
561	L. I. C.	45	F	+	Arteriosclerosis	Ibid.
562	L. A. C.	18	F	+	Mycotic embolism	Ibid.
563	R. M. C.	43	F	+	Arteriosclerosis	Ibid.
564	L. I. C. at P. Comm.	75	F	—	Arteriosclerosis	Ibid.
565	R. I. C.	52	F	—	.....	Cushing: Guy's Hosp. Rep. **73**: 159, 1923
566	L. I. C.	36	F	+	.....	Ibid.
567	R. I. C. at A. C.	36	M	+	.....	Ibid.
568	.....	45	F	..	.....	Cutler: Arch. Ophth. **52**: 331, 1923
569	L. I. C.	65	F	+	.....	Davis: J. A. M. A. **80**: 380, 1923
570	L. P. Inf. Cereb.	22	M	+	.....	Gillies: M. J. Australia **2**: 37, 1923
571	R. M. C.	24	M	+	Embolic (endocarditis)	Loewenhardt: Deutsche med. Wchnschr. **49**: 439, 1923
572	L. M. C.	29	M	+	Embolic (endocarditis)	Ibid.
573	R. M. C.	31	M	+	Embolic (endocarditis)	Ibid.
574	L. M. C.	29	M	+	Embolic (endocarditis)	Ibid.
575	R. M. C.	22	M	+	Embolic (endocarditis)	Ibid.
576	A. Comm.	42	F	+	"Congenital" aneurysm	Ibid.
577	R. M. C.	34	F	+	"Congenital" aneurysm	Ibid.
578	R. P. Comm.	55	F	+	Arteriosclerosis of vessels of brain	McCordock: Bull. Buffalo Gen. Hosp. **1**: 87, 1923
579	R. I. C. at P. Comm.	52	F	+	.....	Symonds: Guy's Hosp. Rep. **73**: 139, 1923
580	.....	25	M	+	.....	Ibid.
581	R. I. C.	29	M	+	Healthy vessels	Adamson: Glasgow M. J. **102**: 396, 1924
582	R. I. C.	43	F	+	.....	Fitz: Boston M. & S. J. **191**: 521, 1924

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
583	R. I. C. at P. Comm.	..	..	+	Atheromatous vessels	Frazier: Progr. Med., Philadelphia **1**: 54, 1924
584	R. I. C.	60	M	+	.....	Kirby: Am. J. Ophth. **7**: 127, 1924
585	R. I. C.	29	F	+	Healthy vessels	Lowy: Ztschr. f. klin. Med. **98**: 100, 1924
586	L. A. C.	41	F	+	Endocarditis or arteriosclerosis	Ibid.
587	Bas.	47	M	—	.....	Schofield: Guy's Hosp. Rep. **74**: 485, 1924
588	R. M. C.	25	M	+	No atheroma	Sheard: St. Michael's Hosp. M. Bull., Toronto **1**: 55, 1924
589	Bas.	30	M	—	Gummatous arteritis	Smith: Brit. M. J. **1**: 994, 1924
590	R. A. C.	24	M	+	Arteriosclerosis	Symonds: Quart. J. Med. **18**: 93, 1924
591	L. A. C.	30	F	+	Arteriosclerosis	Wallesch: Virchows Arch. f. path. Anat. **251**: 107, 1924
592	R. I. C.	29	F	+	Healthy vessels	Ibid.
593	L. A. C.	41	F	+	Internal sclerosis (endocarditis)	Ibid.
594	R. A. C. at A. Comm.	49	M	+	Arteriosclerosis (endocarditis)	Ibid.
595 to 608	L. M. C. (9 cases)		M (3 cases) F (11 cases)		.....	Ibid.
	R. M. C. (5 cases)		..	..	.....	Ibid.
609	Bas.	..	M	..	.....	Ibid.
610	Bas.	..	M	..	.....	Ibid.
611	Bas.	..	F	..	.....	Ibid.
612 to 614	L. I. C.	..	F (3 cases)		.....	Ibid.
615	R. I. C.	..	F	..	.....	Ibid.
616 to 621	A. Comm.	..	M	..	.....	Ibid.
622 to 623	A. Comm.	..	F	..	.....	Ibid.
624 to 629	L. A. C. (6 cases)		M (4 cases) F (2 cases)		.....	Ibid.
630 to 632	R. A. C.	..	F	..	.....	Ibid.
633 and 634	L. Vert. (2 cases)		M (1 case) F (1 case)		.....	Ibid.
635	R. Vert.	..	F	..	.....	Ibid.
636 to 639	L. P. Comm.	..	F (4 cases)		.....	Ibid.
640	R. P. Comm.	..	F	..	.....	Ibid.
641	L. P. Inf. Cereb.	..	M	..	.....	Ibid.
642	R. P. Inf. Cereb.	..	M	..	.....	Ibid.
643	R. Ophth.	..	F	..	.....	Ibid.
644	L. M. C.	32	M	+	.....	Borchardt: Beitr. z. klin. Chir. **133**: 429, 1925
645	L. I. C.	26	M	+	.....	Ibid.
646	R. I. C.	7	M	—	Infected thrombus	Doring: Med. Klin. **21**: 604, 1925
647	Bas.	17	M	+	"Congenital" aneurysm	Duguid: J. Path. & Bact. **28**: 389, 1925
648	R. Ophth.	35	M	—	Mycotic embolus (endocarditis)	Moore: Tr. Ophth. Soc. U. Kingdom **45**: 490, 1925
649	L. Vert.	50	M	+	.....	Packard and Zabriskie: J. A. M. A. **85**: 1633, 1925
650	R. M. C.	21	M	+	.....	Ibid.
651	Bas.	23	M	+	.....	Ibid.
652	Bas.	..	..	..	.....	Ibid.
653	R. M. C.	23	M	+	.....	Conway: Brit. J. Ophth. **10**: 78, 1926
654	L. Vert.	40	F	—	Atheroma	Ibid.
655	R. M. C.	23	M	+	.....	Ibid.
656	L. M. C.	23	F	+	.....	Ibid.
657	L. M. C.	39	M	+	Healthy vessels	Ibid.
658	L. A. C.	40	M	—	.....	Ibid.
659	L. A. C.	53	M	+	Atheroma of vessels	Ibid.
660	R. A. C.	Young	F	+	Healthy vessels	Ibid.
661	R. M. C.	27	M	+	Healthy vessels	Ibid.
662	R. A. C.	45	M	+	Healthy vessels	Ibid.
663	R. M. C.	Middle-aged	M	+	Healthy vessels	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
664	M. C.	41	F	+	Healthy vessels	Conway: Brit. J. Ophth. **10**: 78, 1926
665	L. M. C.	50	M	+	Atheroma	Ibid.
666	R. Vert.	40	F	..	Atheroma	Ibid.
667	A. Comm.	49	F	+	Arteriosclerosis	Ibid.
668	A. Comm.	38	M	+	Healthy vessels	Ibid.
669	L. M. C.	42	M	+	Arteriosclerosis	Ibid.
670	A. Comm.	43	F	+	Healthy vessels	Ibid.
671	L. M. C.	17	M	+	Healthy vessels	Ibid.
672	R. M. C.	23	M	+	Healthy vessels	Ibid.
673	L. M. C.	55	F	+	Atheroma	Ibid.
674	R. M. C. at P. Comm.	23	M	—	Slight atheroma	Ibid.
675	A. Comm.	30	F	+	Vessels healthy	Ibid.
676	A. Comm.	52	F	+	Atheroma	Ibid.
677	Bas.	52	M	+	.....	Ibid.
678	R. M. C.	46	F	+	Vessels healthy	Ibid.
679	R. A. C.	72	M	+	Arteriosclerosis	Ibid.
680	R. M. C.	46	F	+	Vessels healthy	Ibid.
681	Bas.	42	M	+	Atheroma	Ibid.
682	L. A. C.	47	M	+	Vessels healthy	Ibid.
683	L. M. C.	16	M	+	Vessels healthy	Ibid.
684	R. M. C.	69	M	+	Atheroma	Ibid.
685	L. A. C.	32	F	+	Vessels healthy	Ibid.
686	L. M. C.	35	F	+	Vessels healthy	Ibid.
687	Bas.	Boy	M	+	Vessels healthy	Ibid.
688	Bas.	26	F	+	Vessels healthy	Ibid.
689	M. C.	41	F	+	Vessels healthy	Ibid.
690	R. A. C.	41	M	+	Vessels healthy	Ibid.
691	L. M. C.	62	F	+	Atheroma	Ibid.
692	L. M. C.	64	M	+	Atheroma	Ibid.
693	R. A. C.	Young Adult	M	+	Vessels healthy	Ibid.
694	R. A. C.	38	F	+	Vessels healthy	Ibid.
695	L. M. C.	Old	M	+	Vessels healthy	Ibid.
696	M. C.	16	F	+	Vessels healthy	Ibid.
697	L. I. C.	45	F	+	.....	Greene: J. Ophth., Otol. **30**: 106, 1926
698	R. I. C.	32	F	—	.....	Demay, Bertrand and Perisson: Rev. neurol. **1**: 1027, 1926
699	L. I. C. at P. Comm.	73	F	+	Many sclerotic plaques	Jacques: Arch. Path. & Lab. Med. **15**: 122, 1926
700	Bas.	36	M	—	"Syphilitic"	Odqvist: Acta med. Scandinav. **63**: 286, 1926
701	L. M. C.	20	M	+	Embolic	Parker: Arch. Neurol. & Psychiat. **16**: 728, 1926
702	L. M. C. at P. Comm.	20	M	+	Aneurysm "congenital" (coarctation of aorta)	Ibid.
703	R. M. C.	52	M	+	Arteriosclerosis	Ibid.
704	R. I. C.	21	M	+	"Congenital" aneurysm	Ibid.
705	R. P. Comm.	23	F	+	.....	Sands: J. Nerv. & Ment. Dis. **64**: 12, 1926
706	L. P. C.	56	F	+	Arteriosclerosis	Sosman and Vogt: Am. J. Roentgenol. **15**: 122, 1926
707	L. I. C.	34	M	+	.....	Ibid.
708	L. I. C.	32	F	+	.....	Ibid.
709	R. I. C.	52	F	+	Many atheromatous beads on other vessels	Ibid.
710	R. I. C.	45	F	+	Arteriosclerosis	Ibid.
711	R. I. C.	52	F	+	.....	Ibid.
712	R. Side	26	F	..	Aneurysm seen at operation	Ibid.
713	R. A. C.	35	M	+	Vessels not diseased	Ibid.
714	R. I. C.	58	F	..	Aneurysm seen at operation	Ibid.
715	P. C.	69	F	+	.....	Ibid.
716	Interpeduncular space	23	F	—	.....	Trommer: Deutsche med. Wchnschr. **52**: 1534, 1926
717	A. C.	11	F	+	"Congenital" aneurysm	Bagley: Arch. Neurol. & Psychiat. **17**: 316, 1927
718	L. I. C. at P. Comm.	39	F	+	Thickening of intima in basilar artery	Hassin: Arch. Neurol. & Psychiat. **17**: 770, 1927
719	L. I. C.	52	F	+	Small foci of early calcification	Lodge, Walker and Stewart: Brit. M. J. **2**: 1179, 1927
720	Bas.	30	F	—	.....	Nonne: Deutsche med. Wchnschr. **53**: 132, 1927

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
721	L. M. C. at P. Comm.	69	F	+	.....	Pollock: M. Clin. North America **11**: 1, 1927
722	I. C.	42	F	+	No other vascular disease	Ibid.
723	R. P. C.	34	M	+	Normal vessels	Reverts: J. Kansas M. Soc. **27**: 408, 1927
724	L. M. C.	40	M	+	"Congenital" aneurysm (coarctation of aorta)	Weber: Proc. Roy. Soc. Med. **20**: 29, 1927
725	L. M. C. at P. Comm.	20	M	+	"Congenital" aneurysm (coarctation of aorta)	Woltman and Shelden: Arch. Neurol. & Psychiat. **17**: 303, 1927
726	Bas.	30	F	—	Vessels slightly thickened	Zador: Ztschr. f. d. ges. Neurol. u. Psychiat. **109**: 716, 1927
727	A. Comm.	42	F	+	.....	Ibid.
728	R. A. C. at A. Comm.	42	M	+	"Congenital" aneurysm	Ibid.
729	L. P. Comm.	52	F	+	.....	Ibid.
730	L. Side	16	M	+	Embolic (endocarditis)	Esser: Ztschr. f. d. ges. Neurol. u. Psychiat. **114**: 208, 1928
731	R. M. C.	60	F	+	Arteriosclerosis	Ibid.
732	A. Comm.	62	F	+	Arteriosclerosis	Ibid.
733	R. M. C.	38	F	+	Arteriosclerosis	Ibid.
734	A. Comm.	66	F	+	Arteriosclerosis	Ibid.
735	R. A. C.	33	M	+	Vessels healthy	Ibid.
736	R. A. C. at A. Comm.	41	F	+	Vessels healthy	Ibid.
737	L. A. C. at A. Comm.	42	M	+	Vessels healthy	Ibid.
738	R. P. C.	25	M	+	"Congenital" aneurysm; no signs of arteriosclerosis	Graff: Guy's Hosp. Rep. **78**: 493, 1928
739	R. M. C.	30	F	+	Patches of atheromatous changes in wall of aneurysm; "congenital"	Green: Quart. J. Med. **21**: 419, 1928
740	R. M. C.	49	F	+	"Congenital" aneurysm	Ibid.
741	R. A. C.	21	M	+	"Congenital" aneurysm (coarctation of aorta); medial defect	Ibid.
742	L. A. C.	46	F	+	Few patches of atheroma on aneurysm	Harris: Brit. J. Ophth. **12**: 15, 1928
743	R. A. C.	28	M	+	.....	MacLean: Lancet **1**: 1229, 1928
744	Bas.	32	M	+	"Syphilis"	Newman: Southwest. Med. **12**: 408, 1928
745-757	A. Comm.	..	M	+ (13 cases)	.....	Szekely: Beitr. z. gerichtl. Med. **8**: 162, 1928
758-793	A. Comm.	..	F	+ (36 cases)	.....	Ibid.
794-797	R. A. C.	10-20; 4	M	+ (4 cases)	.....	Ibid.
798-802	R. A. C.	20-30; 5	F	+ (6 cases)	.....	Ibid.
804-807	L. A. C.	30-40; 21	M	+ (4 cases)	.....	Ibid.
808-812	L. A. C.	40-50; 31	F	+ (5 cases)	.....	Ibid.
813-815	R. M. C.	50-60; 39	M	+ (3 cases)	.....	Ibid.
816-836	R. M. C.	60-70; 41	F	+ (21 cases)	.....	Ibid.
837-842	L. M. C.	70-80; 13	M	+ (6 cases)	.....	Ibid.
843-853	L. M. C.	80-90; 3	F	+ (11 cases)	.....	Ibid.
854-860	Bas.	..	M	+ (7 cases)	.....	Ibid.
861-866	Bas.	..	F	+ (6 cases)	.....	Ibid.
867	R. Vert.	..	M	+ (1 case)	.....	Ibid.
868	R. Vert.	..	F	+ (1 case)	.....	Ibid.
869-876	L. Vert.	..	M	+ (8 cases)	.....	Ibid.
877	L. Vert.	..	F	+ (1 case)	.....	Ibid.
878	R. I. C.	..	M	+ (1 case)	.....	Ibid.
879-881	R. I. C.	..	F	+ (3 cases)	.....	Ibid.
882	L. I. C.	..	M	+ (1 case)	.....	Ibid.
883-887	L. I. C.	..	F	+ (5 cases)	.....	Ibid.
888	R. P. C.	..	F	+ (1 case)	.....	Ibid.
889-891	L. P. C.	..	M	+ (3 cases)	.....	Ibid.
892	L. P. C.	..	F	+ (1 case)	.....	Ibid.
893	R. P. Comm.	..	F	+ (1 case)	.....	Ibid.
894	R. P. Comm.	..	M	+ (1 case)	.....	Ibid.
895	L. P. Comm.	..	F	+ (1 case)	.....	Ibid.
896	R. A. Inf. Cereb.	..	M	+ (1 case)	.....	Ibid.
897-901	.....	..	M	+ (5 cases)	.....	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
902	L. I. C.	59	F	+	Arteriosclerosis	Albl: Fortschr. a. d. Geb. d. Röntgenstrahlen **39**: 890, 1929
903	L. M. C.	33	M	+	.....	Albright: Bull. Johns Hopkins Hosp. **44**: 220, 1929
904	R. I. C.	61	M	+	.....	Aliquo-Mazzei: Boll. d'ocul. **8**: 1187, 1929
905	L. I. C.	34	F	+	.....	Ironside: West London M. J. **34**: 95, 1929
906	.....	32	M	+	.....	Ibid.
907	R. I. C. at P. Comm.	47	F	+	Arteriosclerosis	Sands: Arch. Neurol. & Psychiat. **21**: 37, 1929
908	R. I. C. at P. Comm.	30	F	+	No other pathologic changes	Shore: Arch. Neurol. & Psychiat. **21**: 607, 1929
909	Bas.	60	M	+	Thickened walls	Ibid.
910	R. A. C.	24	F	+	"Congenital" aneurysm	Forbus: Bull. Johns Hopkins Hosp. **47**: 239, 1930
911	P. C.	8	M	+	"Congenital" aneurysm	Ibid.
912	L. M. C.	32	M	+	"Congenital" aneurysm	Ibid.
913	R. M. C.	28	F	+	"Congenital" aneurysm	Ibid.
914	R. A. C.	33	M	+	"Congenital" aneurysm	Ibid.
915	Bas.	77	F	—	Atheroma	Guillain, Schmidte and Bertrand: Rev. neurol. **1**: 795, 1930
916	L. A. C.	49	M	+	.....	Hamilton: M. J. & Rec. **132**: 8, 1930
917	L. M. C.	21	F	+	"Congenital" aneurysm	Harvie and Chase: Canad. M. A. J. **23**: 252, 1930
918	L. M. C.	28	F	+	.....	Jacobi: Med. Klin. **26**: 730, 1930
919	R. I. C.	23	F	+	.....	Steininger: Wien. klin. Wchnschr. **43**: 1062, 1930
920	R. M. C.	51	F	+	Healthy vessels	Ibid.
921	R. I. C. at P. Comm.	31	F	+	Healthy vessels	Bramwell: Edinburgh M. J. **38**: 689, 1931
922	L. M. C.	52	M	+	Arteriosclerosis	Cabot Case 17281, New England J. Med. **205**: 104, 1931
923	L. P. Comm.	Young	F	+	.....	Collier: Brit. M. J. **2**: 519, 1931
924	L. P. Comm.	28	M	+	.....	Dassen: Semana méd. **1**: 1049, 1931
925	R. M. C.	24	M	+	"Congenital" aneurysm	Glass: Brit. M. J. **2**: 57, 1931
926	R. I. C.	20	F	+	"Congenital" aneurysm	Ibid.
927	L. I. C.	58	F	+	.....	Hahn: New England J. Med. **204**: 549, 1931
928	L. A. C.	44	F	+	Slight evidence of arteriosclerosis	Keegan and Bennett: Arch. Neurol. & Psychiat. **26**: 36, 1931
929	R. I. C.	29	F	+	No arteriosclerosis	Ibid.
930	L. I. C. at P. Comm.	46	F	+	Few yellow plaques on basilar artery	Ibid.
931	R. P. Comm.	27	M	+	.....	Ibid.
932	L. Vert.	50	F	—	.....	Ibid.
933	R. Vert.	56	M	+	.....	Ibid.
934	R. M. C.	31	M	+	.....	Ibid.
935	R. A. C. at A. Comm.	29	M	+	Yellow plaques on intima at bifurcation points; (endocarditis)	Ibid.
936	P. C.	34	M	+	Calcareous deposits	Lemmel: München. med. Wchnschr. **78**: 2193, 1931
937	Bas.	27	M	+	"Congenital" aneurysm	Ibid.
938	R. M. C.	46	F	+	Arteriosclerosis	Ibid.
939	A. Comm.	33	F	+	"Congenital" aneurysm	Read and Gleave: Brit. M. J. **1**: 445, 1931
940	L. I. C.	40	F	+	.....	Sachs: Diagnosis and Treatment of Brain Tumors, St. Louis, C. V. Mosby Company, 1931, p. 325
941	L. A. C.	23	F	+	"Congenital" aneurysm	Schmidt: Brain **53**: 489, 1931
942	R. M. C.	26	M	+	"Congenital" aneurysm	Ibid.
943	L. I. C.	70	M	+	Arteriosclerosis	Ibid.
944	L. M. C.	55	M	+	Arteriosclerosis	Ibid.
945	A. Comm.	72	F	+	Arteriosclerosis	Ibid.
946	L. A. C.	..	F	+	Walls of aneurysm arteriosclerotic	Ibid.
947	R. I. C. at P. Comm.	60	F	+	Very sclerotic	Ibid.
948	R. P. Comm.	64	F	+	Some thickening of intima, probably of infectious origin	Ibid.
949	L. I. C.	49	F	+	Arteriosclerosis	Ibid.
950	L. M. C.	11	M	+	"Congenital" aneurysm	Ibid.
951	L. Ophth.	64	F	—	Arteriosclerosis	Ibid.
952	Bas.	75	M	—	.....	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
953	Bas.	49	M	+	Very sclerotic	Schmidt: Brain **53**: 480, 1931
954	Bas.	66	M	+	Arteriosclerosis	Ibid.
955	R. M. F.	53	F	+	"Congenital" aneurysm	Ibid.
956	R. I. C.	40	F	+	"Congenital" aneurysm	Ibid.
957	R. M. C.	66	F	+	Arteriosclerosis	Ibid.
958	L. M. C.	64	F	+	Arteriosclerosis	Ibid.
959	R. M. C.	..	..	+	Arteriosclerosis	Ibid.
960	R. I. C.	38	M	+	Arteriosclerosis	Ibid.
961	L. M. C.	28	F	+	"Congenital" aneurysm	Voncken: Frankfurt. Ztschr. f. Path. **42**: 481, 1931
962	Bas.	67	M	+	.....	Andreucci: Policlinico (sez. prat.) **38**: 1394, 1932
963	R. M. C.	30	F	+	"Congenital" aneurysm	Chase: J. Path. & Bact. **35**: 19, 1932
964	Bas.	47	M	+	.....	Cushing: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, case 8, p. 196
965	L. I. C. at P. Comm.	47	F	+	.....	Dott: Tr. Med.-Chir. Soc. Edinburgh, 1932-1933, p. 219; in Edinburgh M. J., December 1933
966	R. M. C.	56	F	+	Extensive atheroma	Ibid.
967	R. A. C. at A. Comm.	58	M	—	Arteriosclerosis	Ibid.
968	L. A. C.	36	F	+	.....	Ibid.
969	R. P. Comm.	29	M	+	.....	Elmer and Boylan: M. J. & Rec. **135**: 557, 1932
970	R. I. C. at P. Comm.	25	F	+	No other abnormalities of vessels	Francischetti: Riv. oto-neuro-oftal. **9**: 482, 1932
971	A. Comm.	..	..	+	.....	Freeman: M. Ann. District of Columbia **1**: 208, 1932
972	A. Comm.	..	..	+	.....	Ibid.
973	M. C.	..	..	+	.....	Ibid.
974	M. C.	..	..	+	.....	Ibid.
975	L. A. C.	52	M	+	"Congenital" aneurysm	Grun: Deutsche Ztschr. f. Nervenh. **127**: 205. 1932
976	L. M. C.	25	M	+	"Congenital" aneurysm	Ibid.
977	L. M. C.	61	M	+	Basilar artery arteriosclerotic	Ibid.
978	Bas.	61	F	—	Arteriosclerosis	Ibid.
979	Bas.	24	M	+	Mycotic	Hansmann and Schenken: Am. J. Path. **8**: 435, 1932
980	M. C.	41	F	+	"Congenital" aneurysm	Harper: Brit. M. J. **1**: 13, 1932
981	A. Comm.	19	F	+	.....	Howell: St. Barth. Hosp. J. **39**: 130, 1932
982	Bas.	43	..	—	Atheroma	Kuhn: Arch. argent. de neurol. **7**: 32, 1932
983	A. Comm.	45	..	—	Arteriosclerosis	Ibid.
984	M. C.	35	M	+	Arteriosclerosis	Ibid.
985	R. M. C.	20	F	+	.....	Neurological Clinic Reports [Massachusetts General Hospital], 1932, autopsy 6626
986	R. A. C.	6	F	+	Other vessels normal	Ortmann: Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**: 604, 1932
987	L. P. Comm.	43	M	+	Arteriosclerosis of circle of Willis	Sai and Constantinides: Riv. di neurol. **5**: 449, 1932
988	L. A. C. at A. Comm.	60	M	+	Atheroma of vessels	Ibid.
989	R. M. C.	54	F	+	Pronounced degenerative changes in all coats	Strauss, Globus and Ginsberg: Arch. Neurol. & Psychiat. **27**: 1080, 1932
990	L. M. C. at P. Comm.	61	F	+	Arteriosclerosis	Ibid.
991	Large pial vessel	68	M	+	Arteriosclerosis	Ibid.
992	Bas.	40	M	+	Arteriosclerosis	Ibid.
993	L. P. Comm.	36	F	+	Arteriosclerosis	Ibid.
994	L. A. C.	31	M	+	Diffuse degenerative changes in all three coats	Ibid.
995	L. M. C.	19	F	+	Mycotic (endocarditis)	Ibid.
996	Bas.	17	M	—	Changes of early arteriosclerosis	Ibid.
997	L. P. C.	30	F	—	Arteriosclerosis	Ibid.

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
998	L. I. C.	24	M	+	.....	Biemond and ter Braak: Deutsche Ztschr. f. Nervenh. **132**: 4, 1933
999	L. I. C.	45	F	+	.....	Ibid.
1000	R. A. C. at A. Comm.	40	M	+	.....	Black: M. J. Australia **1**: 434, 1933
1001	R. A. C.	29	M	+	"Congenital" aneurysm	Cabot case 19152, New England J. Med. **208**: 800, 1933
1002	L. I. C.	20	F	+	"Congenital" aneurysm	Cabot case 19451, New England J. Med. **209**: 961, 1933
1003	R. A. C.	29	M	+	"Congenital" aneurysm	Neurological Clinic Reports [Massachusetts General Hospital], 1933, autopsies 6870, 6919 and 6957
1004	A. Comm.	40	M	..	Arteriosclerosis	Ibid.
1005	R. M. C.	..	M	+	Probably "congenital" origin	Ibid.
1006	R. P. C.	28	F	+	Little evidence of infection	Menninger and Dixon: J. Kansas M. Soc. **34**: 343, 1933
1007	.....	35	F	—	.....	Nattrass: Lancet **2**: 915, 1933
1008	L. I. C.	53	M	—	Arteriosclerosis; thickened, calcified vessels on right	Saphir: Am. J. Ophth. **16**: 110, 1933
1009	L. I. C.	57	M	—	Marked arteriosclerosis	Ibid.
1010	L. I. C.	67	M	—	Marked arteriosclerosis	Ibid.
1011	L. I. C.	75	M	—	Marked arteriosclerosis	Ibid.
1012	.....	39	F	+	.....	Tuthill: Arch. Path. **16**: 630, 1933
1013	R. I. C.	47	M	+	Arteriosclerotic changes	Ibid.
1014	R. A. C. at A. Comm.	83	M	—	.....	Ibid.
1015	L. M. C.	42	M	+	Arteriosclerotic changes	Ibid.
1016	L. M. C.	28	M	+	Localized areas of fat absorption	Ibid.
1017	R. I. C.	67	M	+	Cerebral vessels thin and smooth	Ibid.
1018	Bas.	27	M	+	No other microscopic changes; Heubner's arteritis	Volante: Gior. d. r. Accad. di med. di Torino **96**: 233, 1933
1019	A. Comm.	47	M	+	Arteriosclerosis	Ibid.
1020	R. A. C.	76	M	—	Arteriosclerosis	Ibid.
1021	R. M. C. at P. Comm.	69	F	..	Arteriosclerosis	Ibid.
1022	L. I. C.	51	F	+	Vessels degenerated	Yearsley and Piggot: Lancet **1**: 801, 1933
1023	R. M. C. at P. Comm.	37	F	+	.....	Birch: Post-Grad. M. J. **10**: 366, 1934
1024	R. M. C.	47	F	+	.....	Ibid.
1025	R. M. C. at P. Comm.	59	F	..	.....	Ibid.
1026	R. I. C. at P. Comm.	31	F	+	Other arteries healthy	Bramwell: Tr. Ophth. Soc. U. Kingdom **54**: 205, 1934
1027	A. Comm.	42	M	+	"Congenital" aneurysm	Cabot Case 20171, New England J. Med. **210**: 918, 1934
1028	L. M. C.	43	F	+	Arteriosclerosis	Garvey: Arch. Ophth. **11**: 1032, 1934
1029	R. I. C.	54	M	+	Arteriosclerosis	Ibid.
1030	R. I. C.	55	F	—	Intimal thickening	Ibid.
1031	R. I. C.	64	F	+	Thickening of intima and thinning of media	Ibid.
1032	L. M. C.	38	F	+	"Congenital" aneurysm	Kersley: Brit. M. J. **1**: 376, 1934
1033	R. A. Comm. and A. C.	43	M	+	"Congenital" aneurysm	Leopold: Arch. Neurol. & Psychiat. **31**: 605, 1934
1034	A. Comm.	42	M	+	.....	Markovitz: Ztschr. f. Kreislaufforsch. **26**: 512, 1934
1035	R. I. C.	62	F	+	Arteriosclerosis	Neurological Clinic Reports [Massachusetts General Hospital], 1934, autopsies 7174 and 7350
1036	A. Comm.	42	M	+	No arteriosclerosis of aneurysm	Ibid.
1037	L. A. C.	49	M	+	"Congenital" aneurysm	Merritt and Staricoff: M. J. Australia **2**: 387, 1934
1038	L. M. C.	53	M	+	Much arteriosclerosis	van Rijssel: Nederl. tijdschr. v. geneesk. **78**: 3840, 1934
1039	R. I. C.	24	F	+	No arteriosclerosis	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
1040	R. I. C.	50	M	+	No arteriosclerosis	Ibid.
1041	R. I. C.	57	F	+	No arteriosclerosis	Ibid.
1042	R. M. C.	40	F	+	Slight arteriosclerosis	van Rijssel: Nederl. tijdschr. v. geneesk. **78**: 3840, 1934
1043	R. I. C.	51	M	+	No arteriosclerosis	Ibid.
1044	R. P. Comm.	55	F	+	Slight arteriosclerosis	Ibid.
1045	R. P. C.	53	F	+	No arteriosclerosis	Ibid.
1046	R. I. C.	39	F	+	No arteriosclerosis	Ibid.
1047	L. M. C.	60	M	+	No arteriosclerosis	Ibid.
1048	L. M. C.	26	M	+	No arteriosclerosis	Ibid.
1049	R. I. C.	53	M	—	Healthy vessels	Bufano: Policlinico (sez. med.) **42**: 1, 1935
1050	L. I. C.	44	M	+	.....	Neurological Clinic Reports [Massachusetts General Hospital], 1935, cases 96 and 97
1051	R. I. C. at P. Comm.	64	F	+	.....	Ibid.
1052	R. I. C.	43	F	—	.....	Olloz: Schweiz. Arch. f. Neurol. u. Psychiat. **35**: 123, 1935
1053	Bas.	33	F	+	"Congenital" aneurysm	Wagener and Foster: Proc. Staff Meet., Mayo Clin. **10**: 225, 1935
1054	R. M. C.	38	M	+	No other abnormalities	Currier and Davis: J. Michigan M. Soc. **35**: 25, 1936
1055	R. Vert.	45	F	+	.....	Ibid.
1056	R. P. Comm.	20	F	+	Chronic vascular syphilis (?)	Frazier: Surg., Gynec. & Obst. **62**: 1, 1936
1057	L. I. C.	53	M	+	Arteriosclerosis	Ibid.
1058	L. A. C.	44	F	+	Arteries covered with yellow plaques; seen at operation	Gardner: S. Clin. North America **16**: 1019, 1936
1059	R. I. C.	48	M	+	.....	Ibid.
1060	R. M. C.	65	M	—	"Congenital" aneurysm	Lyall: Brit. M. J. **2**: 283, 1936
1061	L. I. C.	57	F	—	.....	McKendree and Doshay: Bull. Neurol. Inst. New York **5**: 223, 1936
1062	R. I. C.	46	F	+	.....	Ibid.
1063	L. I. C.	31	F	—	.....	Ibid.
1064	R. I. C. at P. Comm.	31	M	+	.....	Robertson: M. J. Australia **2**: 381, 1936
1065	L. P. Comm.	61	M	+	Atheroma and congenital defect of media at bifurcation	Ibid.
1066	R. M. C.	31	M	+	Atheroma	Ibid.
1067	A. Comm.	74	M	+	Atheromatous	Ibid.
1068	L. M. C.	28	M	+	.....	Ibid.
1069	R. M. C.	22	M	+	Wall of aneurysm showed diffuse inflammation, of mycotic origin	Ibid.
1070	.....	58	M	—	.....	Sjöqvist: Nervenarzt. **9**: 233, 1936
1071	A. Comm.	50	F	+	.....	Thomas: Ann. d'anat. path. **13**: 969, 1936
1072	L. I. C.	39	F	+	Inflammation of intima	Wetzel: Am. J. Ophth. **19**: 1053, 1936
1073	Vert. (both) at Bas.	35	M	+	Syphilis	Maass: Beitr. z. path. Anat. u. z. allg. Path. **98**: 307, 1937
1074	R. Vert.	..	F	+	Syphilis	Ibid.
1075	R. M. C.	51	F	+	Syphilis	Ibid.
1076	A. C.	38	F	+	Syphilis	Ibid.
1077	P. C. (both)	65	F	+	Syphilis	Ibid.
1078	A. Comm.	50	M	+	Syphilis; yellow plaques on vessels	Ibid.
1079	R. M. C.	69	F	+	Syphilis; slight atheroma	Ibid.
1080	Bas.	73	F	—	Syphilis	Ibid.
1081	M. C.	6	F	+	Infective (endocarditis)	Cleland: M. J. Australia **2**: 141, 1937
1082	.....	20	M	+	.....	Ibid.
1083	.....	28	M	+	.....	Ibid.
1084	.....	36	M	+	.....	Ibid.
1085	.....	39	M	+	.....	Ibid.
1086	.....	49	M	+	Atheroma	Ibid.
1087	.....	54	M	+	.....	Ibid.
1088	.....	58	M	+	.....	Ibid.
1089	.....	62	M	+	.....	Ibid.
1090	.....	67	M	+	.....	Ibid.
1091	A. Comm.	75	M	+	Atheroma	Ibid.
1092	.....	20	F	+	.....	Ibid.
1093	.....	34	F	..	.....	Ibid.
1094	.....	48	F	..	.....	Ibid.
1095	.....	51	F	..	.....	Ibid.

Reference Bibliography with Clinical Data for 1,125 Cases of Intracranial Aneurysms—Continued

No.	Arteries Involved	Age, Yr.	Sex	Rupture	Appearance of Arteries at Base of Brain	Author and Reference
1096	.....	61	F	..	.....	Cleland: M. J. Australia **2**: 141, 1937
1097	.....	62	F	..	.....	Ibid.
1098	.....	71	M	—	Atheroma	Ibid.
1099	.....	46	F	—	.....	Ibid.
1100	Bas.	63	F	—	.....	Dandy: J. A. M. A. **108**: 931, 1937
1101	R. A. Comm.	62	F	+	Atheroma	Dial and Maurer: Am. J. Surg. **35**: 2, 1937
1102	L. I. C. at P. Comm.	54	F	+	Arteriosclerosis	Ibid.
1103	L. I. C.	75	M	+	Arteriosclerosis	Ibid.
1104	R. A. C.	58	F	+	Atherosclerosis	Ibid.
1105	L. I. C.	84	F	—	Atherosclerosis	Ibid.
1106	R. A. C.	37	M	+	Atheroma	Ibid.
1107	R. P. Comm.	72	F	+	Atheroma	Ibid.
1108	L. I. C.	26	F	+	Normal vessels	Ibid.
1109	L. I. C. and A. Comm.	43	F	+	Thickening of wall of internal carotid artery	Ibid.
1110	R. M. C.	49	M	—	Syphilitic arteritis and atheroma	Ibid.
1111	I. C. (both)	49	F	—	Syphilitic arteritis and atheroma	Ibid.
1112	R. Vert.	2	M	+	Congenital (?) narrow media	Ibid.
1113	L. P. Inf. Cereb.	40	M	+	Few small atheromatous plaques; acellular, hyalinized, thin media	Ibid.
1114	.....	8	M	+	No changes in wall; probably septic embolus	Herrman: Am. J. Dis. Child. **53**: 517, 1937
1115	R. P. C.	29	F	+	.....	Jefferson: Brain **60**: 444, 1937
1116	L. I. C.	50	F	—	Aneurysm seen at operation	Ibid.
1117	R. A. C. at A. Comm.	36	F	+	.....	Ibid.
1118	L. I. C.	56	F	—	Aneurysm seen at operation	Ibid.
1119	L. I. C.	23	M	—	Aneurysm seen at operation	Ibid.
1120	.....	44	F	—	Aneurysm seen at operation	Ibid.
1121	R. I. C.	44	M	+	Arteriosclerosis	Jirasek, Henner and Sikl: Mém. Acad. de chir. **63**: 577, 1937
1122	A. Comm. at L. A. C.	32	M	+	.....	McDonald and Korb: Rhode Island M. J. **20**: 91, 1937
1123	R. I. C.	53	F	—	Aneurysm seen at operation	Vincent, Thiebault, Lemoyne and Guillaumat: Rev. neurol. **67**: 361, 1937
1124	R. M. F.	67	F	—	Aneurysm seen at operation	Ibid.
1125	A. Comm.	44	M	—	.....	Wakeley: M. Press **194**: 337, 1937

Comment.—In 1846, Mr. France, an eye surgeon at Guy's Hospital, emphasized the relation between palsy of the third nerve and intracranial aneurysm in a paper entitled "Examples of Ptosis." At autopsy on a patient dying of the "disease ptosis" he observed:

. . . considerable recent extravasation of blood at the base of the brain . . . The hemorrhage had taken place from the posterior communicating artery of the carotid of the right side, through the parietes of which was an aperture, overlaid by a circumscribed clot (termed by some an aneurism) of about the size of

a large pea. Under this the right nerve of the third pair was spread out, having undergone a degree of compression, by this older effusion, more than sufficient to explain the arrested functions of the nerve. Upon section, the tumor proved to be a solid clot.

In discussing 2 similar cases, in which the patient survived, he said:

There can be little doubt that the direct agent in producing the paralysis existed within the cranium; and, in the absence of those more strongly-marked symptoms and more widely-diffused effects, to which meningeal or cerebral inflammation would have given rise; and in the absence of that steadily progressive character of the symptoms for which we look when a tumor is making its stealthy advances; we shall probably not be much in error in assuming . . . the occurrence of a sanguineous or serous effusion or circumscribed vascular enlargement in the vicinity of the nerve of the third pair.

SUMMARY

We have added to the literature 2 cases of intracranial aneurysm with observations at autopsy. In 1 there was an anomaly of the circle of Willis, with a ruptured aneurysm, extensive arteriosclerosis of the cerebral arteries and syphilitic aortitis. In the other there was a ruptured aneurysm of the internal carotid artery, involving the third nerve. We have reviewed 407 articles from the literature from 1761 through 1937, from which we have collected 1,125 cases of saccular aneurysm of the arteries at the base of the brain verified at autopsy or operation. From these cases we have constructed a reference bibliography. The articles are arranged chronologically according to the year of their publication. The cases are numbered, and in each case there are tabulated the artery involved, the age and sex of the patient, whether the aneurysm had ruptured, the appearance of the arteries at the base of the brain, the author of the article and the reference.

APPENDIX

Cases in the literature are listed according to the artery involved by the aneurysm. The numbers following a vessel refer to case numbers in the reference bibliography.

Internal Carotid Artery.—2, 3, 23, 24, 28, 34, 43, 45, 47, 51, 55, 69, 73, 82, 93, 96, 107, 116, 121, 153, 154, 157, 158, 159, 166, 173, 181, 191, 197, 204, 206, 209, 230, 231, 232, 234, 251, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 327, 331, 332, 336, 351, 354, 356, 359, 360, 369, 371, 375, 376, 380, 381, 393, 394, 400, 416, 427, 437, 453, 462, 467, 469, 473, 487, 490, 491, 493, 497, 537, 540, 546, 549, 555, 558, 559, 561, 565, 566, 569, 581, 582, 584, 585, 592, 612, 613, 614, 615, 645, 646, 697, 698, 704, 707, 708, 709, 710, 711, 714, 722, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 902, 904, 905, 919, 926, 927, 929, 940, 943, 949, 956, 960, 998, 999, 1002, 1008, 1009, 1010, 1011, 1013, 1017, 1022, 1029, 1030, 1031, 1035, 1039, 1040, 1041, 1043, 1046, 1049, 1050, 1052, 1057, 1059, 1061, 1062, 1063, 1072, 1103, 1105, 1108, 1111, 1116, 1118, 1119, 1121, 1123.

Middle Cerebral Artery.—11, 12, 13, 19, 20, 21, 31, 53, 57, 63, 64, 75, 78, 79, 83, 87, 88, 95, 100, 102, 103, 106, 108, 110, 111, 112, 113, 117, 118, 119, 123, 124, 127, 128, 129, 130, 133, 134 137, 138, 149, 160, 162, 165, 167, 168, 169, 171, 172, 174, 177, 179, 183, 185, 188, 195, 202, 203, 208, 213, 217, 218, 226, 227, 228, 229, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 250, 252, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 329, 333, 335, 337, 340, 343, 345, 348, 349, 355, 367, 372, 373, 383, 385, 389, 390, 392, 402, 403, 404, 406, 409, 410, 411, 413, 414, 421, 430, 431, 432, 435, 438, 445, 447, 448, 451, 452, 454, 456, 458, 459, 461, 463, 470, 474, 475, 476, 480, 484, 488, 489, 495, 498, 499, 502, 509, 511, 512, 513, 541, 544, 545, 548, 554, 556, 563, 571, 572, 573, 574, 575, 577, 588, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 644, 650, 653, 655, 656, 657, 661, 663, 664, 665, 669, 671, 672, 673, 678, 680, 683, 684, 686, 689, 691, 692, 695, 696, 701, 703, 724, 731, 733, 739, 740, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 903, 912, 913, 917, 918, 920, 922, 925, 934, 938, 942, 944, 950, 957, 958, 959, 961, 963, 966, 973, 974, 976, 977, 980, 984, 985, 989, 995, 1005, 1015, 1016, 1024, 1028, 1032, 1038, 1042, 1047, 1048, 1054, 1060, 1066, 1068, 1069, 1075, 1079, 1081, 1110.

Anterior Cerebral Artery.—6, 7, 8, 25, 58, 76, 98, 115, 131, 180, 224, 275, 276, 277, 278, 279, 280, 361, 378, 386, 407, 420, 429, 446, 450, 494, 523, 562, 586, 590, 591, 593, 594, 624, 625, 626, 627, 628, 629, 630, 631, 632, 658, 659, 660, 662, 679, 682, 685, 690, 693, 694, 713, 717, 735, 741, 742, 743, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 804, 805, 806, 807, 808, 809, 810, 811, 812, 910, 914, 916, 928, 941, 946, 968, 975, 986, 994, 1001, 1003, 1020, 1033, 1037, 1058, 1076, 1101, 1104, 1106.

Anterior Cerebral Artery at Anterior Communicating Artery.—384, 441, 460, 465, 477, 478, 479, 482, 483, 485, 486, 507, 508, 517, 524, 526, 527, 530, 531, 534, 547, 560, 728, 736, 737, 935, 967, 988, 1000, 1014, 1117, 1122.

Anterior Communicating Artery.—10, 72, 89, 101, 139, 146, 156, 163, 164, 176, 186, 193, 199, 222, 223, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 328, 357, 379, 422, 510, 515, 516, 518, 519, 520, 521, 525, 528, 529, 539, 552, 557, 576, 616, 617, 618, 619, 620, 621, 622, 623, 667, 668, 670, 675, 676, 727, 732, 734, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 939, 945, 971, 972, 981, 983, 1104, 1019, 1027, 1034, 1036, 1067, 1071, 1078, 1091, 1125.

Internal Carotid Artery at Anterior Cerebral Artery.—567, 1109.

Internal Carotid Artery at Posterior Communicating Artery.—39, 468, 472, 506, 551, 564, 579, 583, 674, 699, 702, 719, 721, 725, 907, 908, 921, 930, 947, 965, 970, 990, 1021, 1023, 1025, 1026, 1051, 1062, 1102.

Posterior Communicating Artery.—1, 14, 38, 50, 109, 150, 192, 194, 273, 274, 350, 353, 363, 428, 500, 503, 578, 636, 637, 638, 639, 640, 705, 729, 893, 894, 895, 923, 924, 931, 948, 969, 987, 993, 1044, 1056, 1065, 1103.

Posterior Communicating Artery at Posterior Cerebral Artery.—466.

Posterior Cerebral Artery.—32, 42, 60, 66, 68, 124, 136, 142, 178, 210, 233, 397, 412, 433, 436, 496, 522, 550, 553, 706, 715, 723, 738, 888, 889, 890, 891, 892, 911, 936, 997, 1006, 1045, 1077, 1115.

Vertebral Artery.—18, 26, 49, 104, 125, 132, 141, 145, 161, 184, 201, 212, 214, 215, 216, 225, 253, 254, 255, 256, 257 258, 259, 261, 262, 263, 342, 362, 364, 370, 387, 388, 399, 408, 417, 423, 424, 442, 492, 501, 533, 535, 543, 633, 634, 635, 649, 654, 666, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 932, 933, 1055, 1073.

Vertebral Artery at Posterior Inferior Cerebellar Artery.—374.

Basilar Artery.—4, 5, 9, 15, 16, 17, 22, 27, 29, 30, 33, 35, 36, 37, 40, 41, 44, 46, 48, 52, 54, 56, 59, 61 62, 65, 67, 70, 74, 77, 81, 81, 84, 85, 86, 91, 92, 97, 99, 105, 114, 120, 122, 135, 140, 143, 144, 152, 170, 175, 182, 187, 189, 190, 196, 198, 205, 207, 219, 220, 221, 247, 248, 249, 260, 264, 265, 266, 267, 268, 269, 270, 271, 272, 330, 334, 338, 339, 341, 344, 358, 365, 366, 368, 377, 382, 391, 395, 419, 440, 444, 455, 504, 505, 514, 538, 542, 587, 589, 609, 610, 611, 647, 651, 652, 677, 681, 687, 688, 700, 720, 726, 744, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 909, 915, 937, 952, 953, 954, 962, 964, 978, 979, 982, 992, 996, 1018, 1053, 1080, 1100.

Superior Cerebellar Artery.—71, 155.

Anterior Inferior Cerebellar Artery.—398, 418, 426, 464, 895.

Posterior Inferior Cerebellar Artery.—405, 415, 425, 443, 570, 641, 642, 1113.

News and Comment

WISTAR INSTITUTE OF ANATOMY AND BIOLOGY

The Board of Managers of the Wistar Institute of Anatomy and Biology announces the following elections and new appointments:

President, Dr. Esmond R. Long, Director of the Henry Phipps Institute and Professor of Pathology, University of Pennsylvania; Members of the Board of Managers, Dr. Alfred Newton Richards, Vice President Elect in Charge of Medical Affairs and Professor of Pharmacology, University of Pennsylvania, and William H. DuBarry, Vice President and Assistant to the President, University of Pennsylvania; Executive Director, Dr. Edmond J. Farris, Associate in Anatomy in Charge of Operations, The Wistar Institute.

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following certificates were issued at the meeting of the board on May 13 and 14, 1939:

By Examination.—Psychiatry: Anthonisen, Niels L., Boston; Bosselman, Beulah C., Chicago; Boyd, David A., Jr., Ann Arbor, Mich.; Brosin, Henry W., Chicago; Campbell, Coyne H., Oklahoma City; Corson, Harold F., Stockbridge, Mass.; Cushard, William G., Washington, D. C.; † Davis, David B., Grand Rapids, Mich.; DeArmond, A. Murray, Indianapolis; Elgin, William W., Towson, Md.; Erickson, Milton H., Eloise, Mich.; Ewalt, Jack R., Denver; Goduco, Cesarea M., Baltimore, Md.; Goldstein, Richard, New Haven, Conn.; Grogan, Frank M., St. Louis; † Haines, William H., Chicago; Hannett, Frances, Chicago; Hertzman, Jack, Cincinnati; Holmes, Gladys V., Warm Springs, Mont.; Jefferson, Roland A., Milwaukee; Kinley, John W., Asheville, N. C.; Lewis, H. Ryle, Hartford, Conn.; Lippman, Hyman S., St. Paul; † Masten, Mabel G., Madison, Wis.; McCullagh, William H., Jacksonville, Fla.; Moorad, Philip J., New Britain, Conn.; Osgood, Carroll W., Wauwatosa, Wis.; Skorodin, Bernard, Manteno, Ill.; Steegmann, Albert T., Cleveland; Szurek, Stanislaus A., Chicago; † Thorner, Melvin W., Philadelphia; Twombly, Harriet E., Washington, D. C.; Yoder, O. R., Ypsilanti, Mich.

Neurology: Himler, Leonard E., Ann Arbor, Mich.; List, Carl F., Ann Arbor, Mich.; Nash, Cleve C., Dallas, Texas; Thompson, Walter A., Orangeburg, N. Y.; Zeitlin, Howard, Chicago.

Psychiatry and Neurology: Ackerly, Spafford, Louisville, Ky.; Akelaitis, Andrew J., Rochester, N. Y.; Brickner, Richard M., New York; Britt, Robert E., St. Louis; DeJong, Russell N., Ann Arbor, Mich.; Ford, Hamilton F., Galveston, Texas; Gerty, Francis J., Chicago; Golden, Lewis A., New Orleans; Gowan, Lawrence R., Duluth, Minn.; Hughes, Joseph, Philadelphia; Kraines, Samuel H., Chicago; Kubie, Lawrence S., New York; Marker, John I., Davenport, Iowa; Masserman, Jules H., Chicago; McCool, Dick C., Memphis, Tenn.; Miller, Milton L., Chicago; Oliver, Wrenshall A., San Francisco; Patterson, Ralph M., Ann Arbor, Mich.; Rheingold, Joseph C., Chicago; Robinson, G.

† Previously certified in neurology.

Wilse, Jr., Kansas City, Mo.; Shapera, William, Pittsburgh; Solomon, Alfred P., Chicago; Urse, Vladimir G., Chicago; Weiss, Isidore I., Michigan City, Ind.

By Record.—Psychiatry: Ashby, Julian W., Raleigh, N. C.; Conway, Marinus W., Medical Lake, Wash.; Eisler, Edwin R., Chicago; Farr, Clifford B., Philadelphia; Felt, Paul R., Middletown, Conn.; Hall, James K., Richmond, Va.; Herner, William L., Milwaukee; Houston, Angela B., Northampton, Mass.; Hubbard, Lois D., Washington, D. C.; Johnson, Henry L., Supply, Okla.; Riggs, Austen F., Stockbridge, Mass.; Rogers, Lieuen M., Lexington, Ky.; Rounsefell, Clifford G., Wellesley, Mass.; Schumacher, Henry C., Cleveland; Sheets, R. Philip, Traverse City, Mich.; Denison, Charles M., Harrisburg, Pa.; Gilbert, Joseph L., Washington, D. C.; Kanner, Leo, Baltimore; London, Louis S., New York; Oden, John W., Milledgeville, Ga.; Ridout, Lilla, Norristown, Pa.; Salisbury, Frederick S., Knoxville, Iowa; Myers, John W., Albuquerque, N. M.; Wittman, Anthony G., Elgin, Ill.; Yarbrough, Young H., Milledgeville, Ga.

Neurology: *LaMoure, Charles T., Mansfield Depot, Conn.

Psychiatry and Neurology: Chappell, Sidney L., San Francisco; Darden, Oscar B., Richmond, Va,; Kelley, Ernest, Omaha, Neb.; Krauss, Walter H., Spring City, Pa.; Leavitt, Frederick H., Philadelphia; Ley, Charles A., Pittsburgh; Madigan, John J., Ancon, Canal Zone; O'Brien, John D., Canton, Ohio; Powers, Herbert W., Milwaukee; Pilsbury, Lawrence B., San Francisco; Ravine, William, Cincinnati; Sherwood, William D., New York; Smith, Benjamin F., Rochester, Minn.; Tarumianz, Mesrop A., Farnhurst, Del.; Throckmorton, Tom B., Des Moines, Iowa; Weatherby, Francis E., El Paso, Texas; Wilfong, Clavel T., Roanoke, Va.

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* Previously certified in psychiatry.

Abstracts from Current Literature

Anatomy and Embryology

LOCALIZATION IN THE OCULOMOTOR NUCLEI OF THE GOLDFISH. Z. HADIDIAN and MILTON S. DUNN, J. Comp. Neurol. **68**:191 (Feb.) 1938.

This study was undertaken to determine the number and position of the cells in the oculomotor nuclei which supply axons to the individual eye muscles of the goldfish, Carassius auratus. The following operations were performed: removal of one eye and its muscles; complete removal of the contents of both orbits; cutting the nerve to one inferior oblique muscle; cutting individual eye muscles; removal of the cornea, iris and lens without cutting the external muscles, and complete wiping out of the contents of one eyeball. Ninety-seven specimens were studied, 33 of which were controls. The animals were killed from ten to twenty days after the operation. The midbrains were studied after staining for Nissl substance. The oculomotor nuclei consist of from 1,200 to 1,300 cells. About one third of all oculomotor cells supply contralateral muscles. Damage to one muscle results in degeneration of an average of 150 cells. There is no well defined localization for individual eye muscles in the oculomotor nucleus. Hadidian and Dunn conclude that anatomic studies of oculomotor localization are inadequate for understanding the type of coordination present in the muscles of the eyes of the goldfish.

FRASER, Philadelphia.

THE SPINAL ACCESSORY NERVE IN HUMAN EMBRYOS. ANTHONY A. PEARSON, J. Comp. Neurol. **68**:243 (Feb.) 1938.

For this study of the spinal accessory nerves in human embryos, 7 embryos, measuring between 19 and 70 mm., crown-rump length, were available, prepared either by the activated protein silver or the pyridine silver method. Other preparations, stained with toluidine blue and with hematoxylin, were also studied. The cells of origin of the spinal portion of the accessory nerve formed a cell column from the region of junction of the spinal cord with the medulla oblongata into the sixth cervical segment. The intraspinal course of the accessory rootlets was variable, as was the course of the spinal accessory trunk within the vertebral canal. Usually the trunk passed through the ganglion of the first cervical nerve. Ganglion cells observed along the course of the accessory nerve suggested to Pearson the presence of a sensory component.

ADDISON, Philadelphia.

FIBER AND CELLULAR DEGENERATION FOLLOWING TEMPORAL LOBECTOMY IN THE MONKEY. R. WAYNE RUNDLES and JAMES W. PAPEZ, J. Comp. Neurol. **68**:267 (Feb.) 1938.

Two monkeys, a mangabey and a baboon, were utilized for this study of the fiber and cellular degeneration following temporal lobectomy. The temporal lobes had been removed in two operations and the animals allowed to live for eighteen and twenty-six months, respectively, after the first operation. Alternate sections were stained by the Pal-Weigert and by the cresyl violet method. Commissural fibers between the temporal lobes passed by way of the anterior commissure and the corpus callosum. Fibers from the medial geniculate nucleus terminated in the part of the temporal cortex concealed in the sylvian fissure. The optic radiations from the lateral and macular portions of the lateral geniculate nucleus were interrupted. Thalamocortical fibers were observed passing from the pars arcuata of the ventral nucleus to the subcentral and lower postcentral gyri. Striopallidal and strionigral fibers from the tail of the caudate nucleus and from the caudal portions of the putamen were observed.

ADDISON, Philadelphia.

EFFERENT CONNECTIONS OF THE FLOCCULONODULAR LOBE IN MACACA MULATTA. ROBERT S. DOW, J. Comp. Neurol. **68**:297 (April) 1938.

This study was carried out to determine the efferent connections of the flocculonodular lobe of the cerebellum of Macaca mulatta. Experimental lesions were produced in this lobe by use of the Horsley-Clarke stereotaxic instrument. After fourteen days the animals were killed and the brains treated by the Marchi technic. Fibers from the cortex of the flocculus were traced medially into its peduncle. The fibers then divided, one group terminating in the dorsolateral part of the lateral vestibular nucleus of Deiters, the other group in the superior vestibular nucleus of Bechterew. Fibers from the nodulus and uvula ended in all the homolateral vestibular nuclei and in the fastigial nucleus, and a few fibers crossed to the opposite medial longitudinal fasciculus and the dorsal reticular formation.

ADDISON, Philadelphia.

THE RELATIONS OF THE FASCIA DENTATA, HIPPOCAMPUS AND NEOCORTEX, AND THE NATURE OF THE SUBICULUM. A. A. ABBIE, J. Comp. Neurol. **68**:307 (April) 1938.

Abbie has considered the relations of the fascia dentata, the hippocampus and the neocortex in a group of primitive mammals comprising two monotremes, Tachyglossus aculeatus and Ornithorhynchus anatinus; a marsupial, Perameles nasuta, and two placental mammals, Erinaceus europeus and Rattus rattus. In all animals examined the granule cell lamina of the fascia dentata, the pyramidal cell lamina of the hippocampus and all the cell laminas of the adjoining neocortex, at their first appearance, are nothing more than simple localized differentiations within a single continuous layer of cells disposed superficially on the medial surface of the hemisphere. This is the primary stage in hippocampal development. The secondary stages are regarded by Abbie to be the outcome of mechanical factors for the most part. The subiculum may assume one of three forms: (*a*) wider spacing of the cells without disturbance of the continuity of the cell laminas; (*b*) wider spacing of the cells with interruption of the continuity of the most superficial cell lamina; (*c*) wider spacing of the cells with interruption of continuity of the most superficial cell laminas and assimilation of these with the deeper laminas, so that all the hippocampal pyramids become continuous with the deeper neocortical laminas only. Abbie endorses the use of the term "parahippocampal pallium" for the neocortex adjoining the hippocampus in mammals and believes that the hippocampus and the parahippocampal pallium are both derived from a common ancestral primordium.

ADDISON, Philadelphia.

STUDY OF THE NISSL PATTERN IN THE MOTOR CELLS OF THE HIND BRAIN OF THE LIZARD (TACKYDROMUS SEPTENTRIONALIS) UNDER VARIOUS CONDITIONS. WEI CHEN CHOW, J. Comp. Neurol. **68**:335 (April) 1938.

Chow has studied the Nissl bodies in the motor nerve cells in the medulla oblongata of the lizard after the animals had been subjected to different temperatures—some to normal temperatures which induced activity, others to hibernating temperatures and still others to temperatures between 1 and 5 C.—for from two to three weeks. The Nissl substance in the motor cells of animals which were taken during the active period, from April to October, was comparatively abundant. Animals taken during normal hibernation, at a temperature of about 6 C., showed smaller Nissl bodies, arranged in fine granules and loosely aggregated flakes. Distintegration of Nissl bodies showed clearly in animals kept in an ice chamber for two weeks and had progressed even further in three weeks, although the animal survived if returned to room temperature.

FRASER, Philadelphia.

STUDIES ON THE DEVELOPING BEHAVIOR OF ANURA. KARL ARDEN YOUNGSTROM, J. Comp. Neurol. **68**:351 (April) 1938.

Three hundred specimens of anuran embryos and larvae, representing seven species of Anura, were tested for muscular contractions and then preserved in Fol's fixative. The embryos showed considerable neurofibrillation by the time they responded to light touch by a fine human hair. The first general cutaneous fibers grew out from cell bodies located in the neural tube. By the time definite individual withdrawal reflexes appeared in the leg numerous free nerve endings were seen in the epidermis. The arms became motile from three to five days before the legs, but the development of sensitivity to light touch lagged in the arms. Youngstrom's observations on Anura correlate with those of Coghill on Amblystoma.

ADDISON, Philadelphia.

A NERVOUS STRUCTURE IN THE PINEAL BODY OF THE MONKEY. PAUL M. LEVIN, J. Comp. Neurol. **68**:405 (June) 1938.

Eleven pineal bodies from four species of monkeys were studied after having been stained for Nissl substance or myelin. In the posterior two thirds of the pineal body was seen a structure distinct from the pineal parenchyma. Scattered within this structure were numerous well formed ganglion cells and myelinated fibers. Bundles of heavily myelinated fibers were seen to connect this structure with the posterior and habenular commissures, and in 1 specimen with the nerves of the tela choroidea. Because of the presence of myelin, Levin believes that these fibers are not sympathetic.

ADDISON, Philadelphia.

ANTERIOR REGENERATION IN THE EARTHWORM, EISENIA, IN THE CERTAIN ABSENCE OF CENTRAL NERVOUS TISSUE AT THE WOUND REGION. P. L. BAILEY JR., J. Exper. Zoöl. **80**:287 (March) 1939.

In the earthworm, Eisenia foetida, Savigny, the ventral nerve cord was severed in segment 5 and turned back so that the anterior looped end of the cord lay between segments 7 and 8. Then the first five anterior segments were amputated. A head with new cephalic ganglion and ventral nerve cord regenerated in 29 of 55 worms that survived. The new nerve tissue arose autogenously in the regenerate. No evidence was obtained as to whether nerve tissue arose first and induced the differentiation of the other tissues at the region of the wound or whether it arose simultaneously with the other tissues.

WYMAN, Boston.

THE PRODUCTION OF PIGMENT BY CHICK NEURAL CREST IN GRAFTS TO THE 3-DAY LIMB BUD. FRANCES DORRIS, J. Exper. Zoöl. **80**:315 (March) 1939.

Embryos of single comb white leghorns, australorps (a black fowl) and Rhode Island reds were used. Grafts of the neural crest from early somite stages were implanted into the limb bud mesenchyme of 72 hour host embryos. All possible combinations of the three breeds were made. The results justified the following conclusions: Pigmentation in black fowls results from the distribution throughout the dermis and feathers of independently differentiating melanophores of neural crest origin. Pigmentation in red fowls results from the presence of neural crest derivatives which show dependent differentiation. Such cells depend for their final color on factors, probably nonspecific, derived from the host epidermis. The genetic inhibitor for pigment present in white fowls appears to be localized in the epidermis, its effect being quantitative rather than qualitative and increasing in strength during embryonic development. Red or white graft tissue in a black host is masked by dense black pigment, which encroaches on the graft area by cellular invasion. Red host tissue appears to have a specific resistance to tissue from white donors.

WYMAN, Boston.

THE CORTICAL PROJECTION OF THE MEDIAL GENICULATE BODY. H. H. WOOLLARD and A. HARPMAN, J. Neurol. & Psychiat. **2**:35 (Jan.) 1939.

Woollard and Harpman investigated with the Marchi method the distribution of the auditory radiation in the cat following electrolytic lesions at its origin in the medial geniculate body. The lesion was placed in the hilus so that all of the geniculocortical fibers could be destroyed. The authors found that the degenerated fibers start from the place of the lesion, then occupy a field caudal to the lateral geniculate body, from which they pass into the cerebral white matter in a definite fanlike pattern. The ventral fibers from the anterior part of the medial geniculate body traverse the peduncle, while the others enter the internal capsule. The more anterior fibers then traverse the globus pallidus and the putamen, reaching the cortex by traveling around the posterior part of the claustrum. The other fibers reach the cortex by passing caudal to the globus pallidus, putamen and claustrum. The cortical area where the geniculocortical fibers terminate is bounded in front by the anterior ectosylvian fissure, behind by the posterior ectosylvian fissure, above by the suprasylvian fissure and below by the rhinal fissure. The area is traversed axially by the pseudosylvian fissure. The fibers of the geniculocortical tract are entirely homolateral. The lesion failed to produce degeneration in Gudden's commissure, so that in the cat the latter does not arise in the median geniculate body. There was no evidence for the existence of a geniculothalamic tract, nor were there fibers distributed to parts of the cortex other than the cortical area named. In the cat there is no angulation or spiral twisting of the fibers of the auditory radiation near the cortex. The termination of the mesial fillet in the pars externa of the ventral nucleus of the thalamus is such that the fasciculus cuneatus occupies its more medial part.

MALAMUD, Ann Arbor, Mich.

Physiology and Biochemistry

SYMPATHETIC VASODILATOR FIBERS IN THE UPPER AND LOWER EXTREMITIES. THOMAS J. FATHERREE and EDGAR V. ALLEN, Arch. Int. Med. **62**:1015 (Dec.) 1938.

The authors investigated the presence of vasodilator fibers and the mechanism of indirect vasodilatation induced by heat. There is evidence indicating that an increase in temperature in the blood occurs as a result of its passage through the warmed extremity, inducing vasodilatation in the remaining extremities. The possibility of some product of metabolism which is added to the warmed blood and is capable of producing central vasodilatation has never been disproved.

By obstructing the venous return, the authors found that indirect vasodilatation in the toes and fingers induced by warming another extremity depends on the return of the venous blood from the warmed extremity to the general circulation. They corroborated the observations of other experimenters relative to the point that indirect vasodilatation induced by heat depends on the integrity of the sympathetic nerves supplying the part in which the vasodilatation is produced. Patients with Raynaud's disease were subjected to regional nerve block, which was followed by the observation of indirect vasodilatation from heat. It was concluded that in the sympathetic nerves supplying the lower extremities of patients with Raynaud's disease nerve fibers are present which are a necessary part of the mechanism that results in indirect vasodilatation in a cool environmental temperature. Furthermore, regional nerve block is capable of inactivating these fibers, thus preventing reflex vasodilatation in the digits supplied by them. These fibers cannot be vasoconstrictor, because block of vasoconstrictor nerves prevents the passage of central vasoconstrictor impulses and releases the central vasoconstrictor influences, thus tending to produce rather than to prevent vasodilatation. As the integrity of these fibers is necessary for reflex vasodilatation, the conclusion is drawn that they are vasodilator fibers, which are present in the upper and lower extremities in man.

BECK, Buffalo.

CONCENTRATION OF PROCAINE IN THE CEREBROSPINAL FLUID OF THE HUMAN BEING AFTER SUBARACHNOID INJECTION. H. KOSTER, A. SHAPIRO and A. LEIKENSOHN, Arch. Surg. **37**:603 (Oct.) 1938.

With 122 patients anesthetized by the injection of 150 mg. of procaine hydrochloride into the subarachnoid space, the concentration of the anesthetic was determined at various intervals after the injection: (1) in 60 patients, at the site of injection; (2) in 40 patients, three interspaces above the site of injection, and (3) in 22 patients, in the cisterna magna. The data indicate that the injected anesthetic is distributed rapidly cephalad. The peak concentration reached at a particular level during anesthesia decreases rapidly cephalad, so that in the cisterna magna the concentration of procaine was never above 0.21 mg. per cubic centimeter, and in 14 of 22 samples it was less than 0.02 mg. These findings do not support the assumption that the Trendelenburg position causes concentrated solutions of procaine to flow down to the cisterna as do colored solutions in inanimate models.

GRANT, Philadelphia.

THE RELATIONSHIP OF POLYDIPSIA AND POLYURIA IN DIABETES INSIPIDUS. ROWLAND T. BELLOWS and WILLIAM P. VAN WAGENEN, J. Nerv. & Ment. Dis. **88**:417 (Oct.) 1938.

Bellows and VanWagenen studied the relationship of polydipsia and polyuria in experimental diabetes insipidus by establishing esophageal fistulas in dogs. By this device, such dogs could be given measured and adequate food and water through the esophagus, and all water spontaneously drunk could be collected and measured. By appropriate hypothalamic lesions, diabetes insipidus was produced and found to consist of an initial "temporary" and a subsequent "permanent" period of increased intake and output of water, separated by an interval of normal water balance. In some cases only the first, or temporary, phase was seen, with subsequent resumption of normal water exchange. This temporary phase could be produced by trauma to almost any part of the hypothalamus or pituitary stalk, while the permanent phase followed lesions which interrupted fibers from the supraoptic nuclei to the hypophysis or destroyed the supraoptic nuclei themselves.

In dogs with esophageal fistulas supplied with normal and constant amounts of food and water, the temporary phase of diabetes insipidus resolved itself into: (1) a period of marked polydipsia, which reached a maximum on the first or second day after operation and lasted about seven days, and (2) a period of slight polyuria, apparent only on the day of operation. The polydipsia of the temporary phase represented true pathologic thirst, greatly in excess of the minor loss occasioned by the slight polyuria. Since the water drunk by such a dog did not reach the stomach, this polyuria must have been due to the lesion in the hypothalamus. In nonfistulous dogs this slight neurogenic polyuria was buried under the extreme diuresis which was secondary to the polydipsia.

The permanent phase of diabetes insipidus in nonfistulous dogs consisted of a concurrent increase in both intake and output of water, which began about the tenth day after operation, reached a maximum about the twenty-first day and remained permanently increased thereafter. This phase could not be produced in the absence of the pars posterior and pars intermedia of the hypophysis. In dogs with esophageal fistulas the permanent phase of diabetes insipidus was shown to consist only of polydipsia. Such dogs exhibited no evidence of polyuria or dehydration while being given amounts of water previously established as normal for each dog. These animals appeared to suffer no ill effects from deprivation of the excessive amounts of water which the nonfistulous dogs obtained. Bellows and VanWagenen further established that nonfistulous dogs with diabetes insipidus exhibit: (1) water intake which exceeds the urinary output; (2) progressive gain in body weight, and (3) obesity, which occurs even in the absence of adiposogenital dystrophy. In diabetes insipidus there is thus chronic cumulative retention of water. The production of primary polydipsia by injury to the

hypothalamus suggested to Bellows and VanWagenen that this region is the center of the thirst function, which therefore seems to be an integral component of the mechanism controlling water metabolism. "The polydipsia of diabetes insipidus may presumably be regarded as the activity of the thirst mechanism as the result of a persistently abnormal variation in the solute content of the body fluids."

MACKAY, Chicago.

THE ARM REFLEXES. G. DE M. RUDOLF, J. Neurol. & Psychiat. **2**:7 (Jan.) 1939.

Rudolf tested the triceps, biceps and supinator reflexes in 466 healthy persons and found absence of one or more of the arm reflexes in 3.6 per cent of persons and in 1.23 per cent of reflexes tested in a single examination. This was found to be more common in persons past the age of 20. Of 600 tests for reflexes in a special group of 100 persons, 74.1 per cent were normal, 5.5 per cent absent, 5.8 per cent diminished and 13.5 per cent increased. Tests for each reflex individually gave about 75 per cent of normal responses. There was a slight tendency for responses to be absent in greater proportion early in the day. Repeated examinations of the reflexes in 7 persons showed little variation from single examinations in the number of normal responses. Cold and exercise either increased or decreased these responses. From 40 to 47 per cent of the variations from the normal were simultaneously bilateral.

MALAMUD, Ann Arbor, Mich.

TOUCH, PAIN AND TICKLING: AN ELECTRO-PHYSIOLOGICAL INVESTIGATION ON CUTANEOUS SENSORY NERVES. YNGVE ZOTTERMAN, J. Physiol. **95**:1, 1939.

Zotterman investigated the axon potentials evoked in cutaneous nerve filaments by heavy stroking of the skin, light touch and burning. Stroking of the skin set up axon potentials in at least four groups of nerve fibers: (1) fibers in which the axon potentials were large and were conducted at rates ranging from 30 to 60 meters per second; (2) fibers with smaller axon potentials conducted at 20 to 30 meters per second; (3) fibers with still smaller axon potentials conducted at about 12 meters per second, and (4) fibers in which the axon potentials were barely detectable in the records and the conduction rate appeared to be slow, although it could not be measured by the method employed. The potentials in the last three groups of fibers outlasted the stimulus for a few seconds.

Very light stroking, interpreted by the author as analogous to tickling, caused axon potentials to appear in the last three groups of fibers. Burning, without any mechanical stimulation of the skin, produced axon potentials in fibers of the same type as those stimulated by light stroking. A needle prick stimulated all four groups of fibers, but the axon potentials in the last three groups appeared only as after-discharge.

The author points out the known relation of size of axon potential, rate of conduction and size of fiber and concludes that the first group of fibers are probably from 10 to 14 microns in diameter, the second group from 7 to 9 microns, the third from 5.5 to 7 microns and the fourth below 5.5 microns. He concludes also that pain is conducted by fibers of small diameter and that burning and tickling sensations are conveyed over the same fibers as pain.

THOMAS, Philadelphia.

SENSATION AND MOTILITY IN DIENCEPHALON-MIDBRAIN PIGEONS SURVIVING FOR A LONG TIME. R. THAUER and G. PETERS, Arch. f. d. ges. Physiol. **240**: 505, 1938.

Pigeons were kept alive for as long as two years after complete extirpation of the cerebrum and striatum. Some of the animals showed normal labyrinthine reflexes and normal acoustic and optic perception, and were able to perform normal movements, such as walking, running and flying. They showed mind blindness,

had no spontaneity and could not feed themselves. In 1 pigeon, however, normal functions returned within two years after extirpation of the forebrain to such an extent that it could be distinguished from a normal animal by careful examination only. It did not show complete mind blindness, had spontaneous reactions and recovered the capacity to feed itself. Histologic examination of the brain in this animal, as well as in the others, showed absence of the forebrain. The brain of the animal with the highest degree of functional restitution differed from the brains of the other pigeons on which operation was performed in that it showed almost no injury to the midbrain and diencephalon. It seems possible, therefore, that some of the disturbances observed in pigeons after extirpation of the cerebrum are due to injuries to the midbrain and diencephalon.

SPIEGEL, Philadelphia.

QUANTITATIVE MICROCHEMICAL DETERMINATION OF ALCOHOL IN THE CEREBROSPINAL FLUID. E. GABRIEL and S. NOVOTNY, Arch. f. Psychiat. **108**:279 (June) 1938.

Gabriel and Novotny examined 44 neurologically normal persons and found that minute quantities of alcohol are present normally in the body fluids. The blood usually contains about 0.037 per cent, whereas the spinal fluid contains about one-fifth that quantity. A number of persons suffering from dementia paralytica and a similar number of schizophrenic patients were given 0.25 liter of a 15 per cent solution of alcohol, and the blood and cerebrospinal fluid were then examined. It was found that, whereas the successively determined alcohol concentrations in the blood were the same for both groups, the quantities in the cerebrospinal fluid were consistently higher in the cases of dementia paralytica, which is in keeping with the observation that the barrier between the blood and the cerebrospinal fluid has a greater permeability in cases of dementia paralytica. At the same time, this finding also supports the theory that alcohol, like a number of other chemical substances, does not enter the cerebrospinal fluid by simple diffusion but that there is a physiologic selection which permits only a certain portion of the substance to permeate. In 4 cases larger quantities of alcohol were administered by intravenous injection. After this, a series of determinations was made on both the blood and the cerebrospinal fluid. The highest degree of concentration was found to be reached in the blood after about ten to twenty minutes and in the cerebrospinal fluid after twenty-five to thirty-five minutes. After this there was a reduction in the concentration, but this took place faster in the blood than in the cerebrospinal fluid. It was found that an increased amount of alcohol in the cerebrospinal fluid can be demonstrated as late as six and one-half hours after injections of alcohol.

MALAMUD, Iowa City.

Neuropathology

THE IRON CONTENT OF THE HUMAN BRAIN. A. H. TINGEY, J. Ment. Sc. **84**: 980 (Nov.), 1938.

Tingey found that in dementia paralytica the total iron varies from 4.57 to 5.75 mg. per hundred grams of fresh tissue, as compared with 2.94 to 4.05 mg. in a normal cortex. Tingey found that there is an excess of available, or non-hematogenic, iron in cases of dementia paralytica, in which there is a definite deposit of iron that can be demonstrated by histochemical tests. This excess of total iron is largely in the pallidum or corpus striatum. The cortex and white matter each contain about 70 per cent of protein iron. The water-soluble, alcohol-ether-insoluble iron constituents about 12 per cent of the iron in the white matter and 25 per cent of the iron in the cortex, corpus striatum and pallidum.

KASANIN, Chicago.

AGENESIS OF THE CORPUS CALLOSUM. J. S. LLOYD, J. Ment. Sc. **84**:995 (Nov.) 1938.

Over 100 cases of agenesis of the corpus callosum are on record. Lloyd reports the case of an idiot girl who died at the age of 9 years, of pneumococcic meningitis. She was microcephalic, the cranial circumference being 17 inches (43 cm.). She had spastic quadriplegia and bilateral atrophy of the optic nerve, with absence of the light reflex. Several degenerative phenomena were in evidence, including facial asymmetry, strabismus, scoliosis and attacks of grand mal. Post mortem, a large fibroma was seen in the wall of the left ventricle of the heart, which almost obliterated the cavity but had given rise to no murmurs or other cardiac signs during life. Examination of the brain revealed pneumococcic meningitis. The cerebral hemispheres were small, weighing only 8½ ounces (240 Gm.) each. Microgyria was absent. On separating the hemispheres, complete absence of the corpus callosum was revealed. No clue was obtained as to the cause of the condition. The family history was unsatisfactory.

KASANIN, Chicago.

DEATH DURING INSULIN TREATMENT OF SCHIZOPHRENIA. STEPHEN A. MACKEITH and A. MEYER, J. Ment. Sc. **85**:96 (Jan.) 1939.

MacKeith and Meyer report a case of death during hypoglycemic treatment of schizophrenia. Pathologically, the changes were characterized by proliferation of the fibrous glia, chiefly within the white matter. There was only slight evidence of typical ischemic necrosis.

KASANIN, Chicago.

MENINGO-ENCEPHALITIS DUE TO CRYPTOCOCCUS MENINGITIDIS (TORULA HISTOLYTICA). J. A. GREENFIELD, J. P. MARTIN and M. T. MOORE, Lancet **2**:1154 (Nov. 19) 1938.

To the 63 cases of cryptococcic meningitis in the literature the authors add the case of a youth aged 18, who complained of headache, giddiness, vomiting, pain in the neck and impaired vision. There was a discharging wound of the right index finger, caused by a minor abrasion. The symptoms grew progressively worse, the pain extending down between the shoulders. Examination gave normal results, except for edematous disks and stiffness of the neck. The temperature ranged from 99.8 to 97.2 F. The spinal fluid pressure was 300 mm. of water; the fluid contained 35 lymphocytes per cubic millimeter, 40 mg. of proteins and 750 mg. of chlorides, per hundred cubic centimeters. The fluid was sterile and contained no tubercle bacilli; no pellicle formed on standing. Smears from the wound in the finger showed Staphylococcus aureus, and a Streptococcus was obtained on culture. Ventriculographic examination disclosed symmetric dilatation of the lateral and third ventricles. Subsequent exploration of the cerebellum revealed a "localized cyst due to circumscribed adhesive meningitis." The patient died seven weeks after the onset of symptoms. Necropsy revealed typical organisms embedded in the meninges in the region of the cisterna magna and cisterna pontis, together with endothelial macrophages, multinucleated giant cells, lymphocytes and occasional plasma cells. Small perivascular infiltrations of these organisms were discovered in the cortical tissue and white matter. The basal ganglia were extensively involved, with many cystlike collections about small blood vessels and a minimal inflammatory reaction in the adjacent parenchyma.

Intracisternal injections of spinal fluid in animals will yield the yeastlike organism in pure culture and will produce lesions of the central nervous system. The condition may be confused with tuberculous meningitis, cerebral tumor or abscess of the brain. The portal of entry is probably the respiratory tract, with the middle ear, nasal sinuses, nasopharynx and intestinal tract playing a secondary role.

KRINSKY, Boston.

FREQUENCY OF GLIOMAS WITH VARIABLE HISTOLOGIC STRUCTURE. H. J. SCHERER, J. belge de neurol. et de psychiat. **38**:783 (Oct.) 1938.

The present classification of gliomas is based on the assumption that these tumors show the same cellular and structural aspects in all areas. The method of prognosis by means of histologic examination of small parts of a glioma removed at operation is based entirely on this premise. Studies on necropsy material, however, show that definite histologic variations in the gliomas are not rare. In 40 of 100 cases of gliomas Scherer observed the presence of two or more structural elements. In one fourth of the cases there was a combination of "benign" and "malignant" glioma tissue. This percentage is so considerable that it invalidates the prognostic value of biopsy of circumscribed bits of tumor tissue.

DE JONG, Ann Arbor, Mich.

ANATOMIC BASIS OF LESSER DEGREES OF VISUAL AGNOSIA. F. LOTMAR, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:299, 1938.

It is generally agreed that visual agnosia of high degree, or mind blindness, is encountered in cases of unilateral lesions involving the left occipital lobe only when the splenium of the corpus callosum is also implicated. It does not seem to have been definitely established, on the other hand, whether lesions limited to the convexity of the left occipital lobe can give rise to lesser degrees of visual agnosia.

A woman aged 73 had suffered a cerebral vascular accident eight months before examination. Her personality was intact, and there appeared to be no gross intellectual defect. An accurate estimate of the patient's ability to recognize objects was difficult because of sensory aphasia and ideational and ideomotor apraxia. Her hesitancy in identifying certain objects and pictures, however, seemed to justify the conclusion that there was visual agnosia of moderate degree. Complete verbal alexia and severe literal alexia were noted, in addition to marked agraphia, which was apparent both in spontaneous writing and in writing to dictation. The patient also showed definite paraphasia and had difficulty in word finding. Studies of the visual fields were unsatisfactory, but there were indications of incomplete right homonymous hemianopia. Though the clinical studies were fairly comprehensive, they were limited to a period of four weeks by the occurrence of further cerebral accidents and myocardial failure.

Postmorten study disclosed a few small areas of recent softening in the right cerebral hemisphere. More extensive softening of recent origin was seen in the medial surface of the left occipital lobe, the inferior surface of the temporo-occipital lobe, the splenium of the corpus callosum and part of the thalamus. As these lesions obviously did not exist when the pertinent clinical observations were made, they were disregarded, and attention was directed to an older lesion on the convexity of the left hemisphere. Grossly, this lesion extended from the region of the angular gyrus, which had been destroyed, into the temporal lobe and across the interparietal sulcus to the superior parietal convolution. On microscopic study of coronal sections, the lesion was seen to involve, in addition to the parts named, the lateral occipital gyri and the posterior half of the supramarginal gyrus. Heschl's gyrus was included in the extensive involvement of the superior and middle temporal gyri, but only the posterior portion of the inferior temporal gyrus was affected. Softening of the lower part of the superior parietal convolution extended forward to the postcentral gyrus. The lesion extended inward to the wall of the posterior horn of the lateral ventricle, but portions of the stratum sagittale externum and stratum sagittale internum lying beneath the ventricle were intact.

Lotmar expresses the view that the visual agnosia of moderate degree was due mainly to destruction of the cortex and white matter of a large portion of the left occipital convexity. Involvement of contiguous areas in the parietal and temporal lobes must have played a subordinate role, since lesions limited

to these parts are not followed by visual agnosia, at least not in the chronic stage. He does not deny, however, that injury to association fibers in the sagittal strata may have had some significance. Involvement of the tapetum, with its contingent of fibers from the corpus callosum, on the other hand, would be of little importance, in view of the marked damage to the lateral occipital gyri in which these fibers terminate. The partial destruction of the tapetum, furthermore, was not sufficiently extensive to sever connections of intact portions of the left occipital lobe with the opposite hemisphere, as would be the case had the splenium been destroyed.

DANIELS, Denver.

Diseases of the Brain

EPILEPSY IN CEREBRAL TUMORS. J. A. CHAVANY and A. PLACA, Presse méd. **46**:1522 (Oct. 15) 1938.

Chavany and Placa state that epilepsy may appear either in typical or in somewhat abnormal forms during any phase of the clinical evolution of cerebral tumors. They encountered it in about 15 per cent of the hundreds of cases studied personally, whereas other investigators have given percentages of 21, 30 and even 41. The authors point out that epilepsy can be observed as a secondary sign, associated with ventricular dilatation or cerebral edema, in all forms of cerebral tumors. It appears in three forms: (1) generalized attacks analogous to those of essential epilepsy; (2) abortive (petit) attacks with short loss of consciousness and without convulsive manifestations, and (3) jacksonian attacks. Frequent jacksonian attacks which remain similar for months or years suggest the existence of a cerebral tumor affecting the pyramidal tract in the neighborhood of its origin. Conversely, in the absence of the syndrome of intracranial hypertension, jacksonian attacks that occur less close together (months apart) and perhaps change their aspect suggest encephalitis; if intracranial hypertension exists, they suggest encephalitis or a tumor of extrapyramidal localization. Although a cerebral tumor can be excluded in the presence of jacksonian attacks that are far apart, polymorphic and not accompanied by intracranial hypertension, in the presence of numerous and identical jacksonian attacks it is impossible to make a distinction between encephalitis and tumor, since encephalitis may also cause such a clinical picture. The generalized epileptic attacks are often without value for localization, except that they are often the first sign of a lesion in a mute zone. In case of abortive (petit) epileptic attacks a temporal localization should be searched for. The jacksonian attacks, which have considerable localizing value, constitute often the alarm signal of compression of the cerebral origins of the pyramidal bundle. A long phase of jacksonian attacks which are more or less close together and constitute the only symptom indicates a malignant tumor. However, it is impossible to distinguish by clinical means alone an extracortical meningioma from an intraparenchymatous fibrous glioma. On the other hand, jacksonian attacks which are less numerous and which precede, accompany or follow the appearance of rapidly progressing hemiplegia of the flaccid type indicate nearly always the existence of a malignant tumor.

J. A. M. A.

HERPETIC ENCEPHALITIDES: APOPLECTIC FORM; CONVULSIVE AND HALLUCINATORY FORM; CONTAGION BY HERPETIC VIRUS. G. DE MORSIER, Presse méd. **46**:1611 (Nov. 2) 1938.

In less than a year de Morsier observed 3 patients in whom grave cerebral disturbances coexisted with an eruption of labial herpes. In the first 2 cases the conditions show close resemblance. The disorder began abruptly; the temperature rose to 39 C. (102.2 F.); the patients fell into coma, which persisted for forty-eight hours, and meningeal symptoms appeared. The first patient showed signs of agitation during the period of coma. In this patient the herpes appeared after two days, whereas in the second it did not appear until the eighth day. With regard

to the cerebrospinal fluid, the author says that in the first case there was no leukocytosis but hyperalbuminosis was present; in the second case polymorphonuclears and moderate hyperalbuminosis were detected. Examination of the blood disclosed in both patients mild leukocytosis without noticeable modification of the leukocytic equilibrium. The evolution was similar in the 2 cases. Eleven days after onset of the coma, both patients could be discharged as cured. In the third case the evolution was analogous to that in the first two, but the symptoms differed in that the cortical type predominated. There were intermittent convulsions with an aura, complex forced movements (nutation) and visual and auditory hallucinations accompanied by a certain degree of amnesia. Severe labial herpes appeared on the fifth day. Examination of the cerebrospinal fluid disclosed no inflammatory reaction, but examination of the blood revealed leukocytosis. All the alarming cerebral symptoms disappeared in about three weeks. The nurse who attended this patient showed typical herpetic keratitis one week after the appearance of the labial herpes. Ophthalmologic examination of the nurse disclosed delicate epithelial vesicles in the central region of the cornea of both eyes. The author finds that the majority of patients present meningeal symptoms. He distinguishes three clinical forms of herpetic encephalitis: (1) the meningeal form, which so far has been observed most frequently and which may be relapsing; (2) the convulsive form with paresthesias and vertigo, and (3) the comatose form with sudden onset. It has been demonstrated that the liquid from herpetic vesicles of human subjects when injected into the cornea of rabbits produces dendritic keratitis. The keratitis can be transmitted from one animal to another. In some of the rabbits in which keratitis has been produced by the inoculation of herpetic material encephalitis develops and may terminate in death. After inoculation with the virus of encephalitis the cornea of rabbits is immune to the herpetic virus. Herpetic virus derived from the brain of a rabbit which has died of experimental herpetic encephalitis and introduced (for therapeutic purposes) into the spinal cavity of a patient with postencephalitic parkinsonism may provoke encephalitis of two or three weeks' duration which is accompanied by a cutaneous herpetic eruption. These therapeutic attempts never resulted in death. The author says that opinions are still divided as to the identity of the virus of encephalitis and herpes. He thinks that there is probably a relation between the herpetic virus and the cerebral symptoms presented by his patients. The fact that herpetic keratitis developed in the nurse indicates the virulence and recalls to the author several small epidemics of herpes, in one of which the disease presented meningitic aspects.

J. A. M. A.

INFLUENCE OF TREATMENT ON THE DEVELOPMENT OF DEMENTIA PARALYTICA. M. GLATT, Confinia neurol. **1**:257, 1938.

In studying a group of patients with dementia paralytica whose symptoms developed between the years 1925 and 1935, Glatt was unable to determine any definite difference in the length of the latent period between cases in which no specific antisyphilitic treatment had been received and those in which treatment had been given in the early stages of the syphilitic infection. He was unable to substantiate the statement that arsphenamine is responsible for shortening the incubation period in dementia paralytica, although intensive treatment with arsphenamine did produce relatively better results. The author was also unable to support the opposite theory, that the modern treatment of syphilis promotes the development of dementia paralytica.

DE JONG, Ann Arbor.

OCULAR ORIGIN OF MIGRAINE IN CHILDREN AND YOUNG PERSONS. K. GRUNERT, München. med. Wchnschr. **85**:1337 (Sept. 2) 1938.

For a period of ten years, Grunert made careful functional tests on the eyes of all patients who were subject to headaches and to migraine and, as far as possible, of the relatives of these patients who were subject to headaches. In the

course of these studies he made two significant observations: 1. In the majority of the patients with headaches and in nearly all those with migraine there existed disturbances in ocular function. 2. Treatment of these ocular disturbances reduced or completely removed the general symptoms to such an extent that a causal connection could not be denied. Among children and young persons the ocular origin of migraine was even more pronounced than it was in adults. The author reports observations in more than 200 cases of migraine in children and young persons. Many of the patients were of the type referred to as "difficult" children; that is, they showed signs of nervous irritability, and they were difficult to manage or were inattentive in school. Ocular examination disclosed defective refraction, disturbances in ocular equilibrium and defects in accommodation. In many of these children the growth of the eyes is not completed as early as in others, and school, requiring a considerable amount of close work, involves a great strain on these still growing eyes. The author emphasizes that even slight optic defects may cause severe subjective disturbances. After the refractive defects have been corrected, close work is avoided for one or two weeks, and the weakened muscle of accommodation is treated with pilocarpine. The administration of pilocarpine must be individualized. It is best to administer it in the evening before the patient goes to sleep. In severe conditions it can be given also during the day, but in this case the individual doses are, of course, smaller. In cases of disturbances in muscular equilibrium or of latent strabismus prisms are employed; occasionally an operation for strabismus may be resorted to or stereoscopic exercises may be utilized. In the few cases in which no anomalies of refraction exist and there is no impairment of muscular equilibrium, but only sufficiency of the apparatus of accommodation, the migraine is cured by resting the eyes for a while and by treatment with pilocarpine. The ocular treatment effected cure in 197 children and young persons with migraine.

EDITOR'S ABSTRACT.

LATE EPILEPSY AFTER CARBON MONOXIDE POISONING. O. SCHIERSMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:656 (Oct.) 1938.

A man aged 60 had been poisoned by carbon monoxide from a running automobile motor when he was 30. He was admitted to the hospital four days after exposure to the gas, without any relevant history in the interval. A toxic delirium was present for fourteen days, after which marked intellectual enfeeblement persisted. He was dull and inactive, lacked initiative and was disoriented when examined. Occasional periods of excitement with irritability recurred. There were some hypomimia and defective associated movements, but no tremor or rigidity, and mild weakness of the face and tongue with dysarthria. The spinal fluid was normal. A few months after the acute intoxication attacks of turning of the trunk appeared, without loss of consciousness. In 1932, fourteen years after the accident, grand mal seizures appeared, with turning of the head to the right and athetoid movements of the left extremities. Marked alexia, agraphia and anomia were noted. Encephalography showed atrophy of the cortex, especially in the frontal poles. The basal ganglia seemed atrophic and poorly outlined. The lateral ventricles and especially the third ventricle were enlarged. The disturbance in language function was probably due to circumscribed lesions of the brain. There was ample evidence of injury to the basal ganglia as seen especially in the torsion movements of the trunk. The late onset of the epileptic attacks is unusual and may be connected with the carbon monoxide poisoning by assuming that this intoxication was a contributory factor in the development of cerebrovascular disease. The role of injury to the subcortex, especially in the hypothalamic region, is emphasized as important in explaining the changes in personality and character. Diffuse cerebral injury accounted for the intellectual enfeeblement.

SAVITSKY, New York.

Diseases of the Spinal Cord

TOXIC MYELOPATHY (SPINOCAINE): SOME CONTRAINDICATIONS TO SPINOCAINE ANESTHESIA. H. KELMAN and G. A. ABBOTT, Ann. Surg. **108**:1001 (Dec.) 1938.

Kelman and Abbott suggest that if spinal anesthesia were not employed for patients with severe myocardial damage, hypertension, marked hypotension, psychoneuroses and congenital anomalies, the number of complications following its use would be diminished. The spinal anesthetics commonly employed have been shown to be both myelolytic and hemolytic. When injected into dogs they produce an aseptic meningeal reaction with an exudation of plasma cells and proliferation of arachnoid cells, which later results in thickening of the meninges, disintegration of axons and degeneration of the peripheral portion of the cord. Somewhat similar changes have been demonstrated in the spinal cords and nerve roots of patients dying after spinal anesthesia (procaine hydrochloride). Spinal anesthesia has about the same immediate mortality and death rate from postoperative pneumonia as has ether anesthesia, but is superior to it in that it produces greater muscular relaxation and does not have the ill effects which follow ether. Almost any part of the central nervous system may be affected, with the involvement remaining permanent or causing fatality, but if the aforementioned contraindications are recognized the complications and mortality incident to spinal anesthesia should become negligible.

J. A. M. A.

SACROCOCCYGEAL TERATOMA IN THE ADULT. J. GRAFTON LOVE and FREDERICK P. MOERSCH, Arch. Surg. **37**:949 (Dec.) 1938.

Sacrococcygeal tumors in adults are rare. They tend to be associated with the presence of rudimentary organs. These growths are derived from more than one germ layer and are usually trigeminal in origin. The site of origin of sacrococcygeal teratoma is probably always retrorectal. The tumor may be attached to the rectum, to the sacrum or to the coccyx. Lumbosacral teratoma is closely related to sacrococcygeal teratoma, but probably originates from a different embryonic focus. The occurrence of teratoma has no relation to sex. In the diagnosis of sacrococcygeal teratoma, it must be recalled that if the tumor is situated anterior to the sacrum it may escape detection for many years. Consequently, in a case in which a sacral growth is suspected a careful rectal examination should be made in addition to the usual roentgenologic studies, as the latter may fail to reveal osseous changes. Chordoma is not infrequently present in the sacrococcygeal region and must be distinguished from teratoma. Other conditions to be considered in the differential diagnosis are tumor of the spinal cord, primary malignant tumor of the pelvis, metastatic growth, pelvic tumor (such as ovarian cyst), fibromyoma, adenoma, rectal fistula, pararectal abscess and, finally, spina bifida and meningocele. De Veer and Browder have laid down the following six points to aid in distinguishing meningocele from teratoma: (1) The skin covering a teratoma is usually normal, while the skin covering a meningocele or a myelomeningocele is embryonal in type; (2) a teratoma is usually large and extends into the pelvis, while a meningocele is small and rarely extends anterior to the sacrum; (3) a teratoma tends to grow more rapidly than does a meningomyelocele; (4) a teratoma is solid and as a rule is not connected with the spinal canal, while a meningocele tends to be softer and contains spinal fluid; (5) in cases of teratoma there are rarely any neurologic complications; in cases of meningocele or meningomyelocele neurologic complications frequently occur; (6) hydrocephalus is a frequent accompaniment of meningocele or meningomyelocele, but it is never associated with a teratoma. Teratoma of the spinal column is not confined to the sacrococcygeal region. It has been observed also in the cervical, thoracic and lumbosacral segments of the spinal cord. Surgical removal of a sacrococcygeal teratoma is always worthy of consideration, and unless there is involvement of the spinal cord the results are exceedingly satisfactory.

GRANT, Philadelphia.

PATHOGENESIS OF FUNICULAR MYELITIS. J. ROTHFELD, Confinia neurol. **1**:243, 1938.

Rothfeld believes that funicular myelitis, or posterolateral sclerosis, is primarily a deficiency disease. Its occurrence in association with pernicious anemia is not a direct result of the anemia but is due to the deficiency of a substance that must be differentiated from the antianemic ferment. It may develop in association with pyloric stenosis or gastric or duodenal ulcer if the individual predisposition exists. The lack of certain amino acids may contribute to the genesis of the spinal symptoms. Rothfeld believes that familial and individual predispositions are important factors in the development of the disorder and that it is necessary to distinguish between a genuine, or heredodegenerative, type of posterolateral sclerosis and the symptomatic type which occurs in pernicious anemia and other deficiency diseases.

DE JONG, Ann Arbor, Mich.

A CASE OF NEUROFIBROMATOSIS RECKLINGHAUSEN COMBINED WITH LATERAL SPINAL MENINGOCELE. A. SCHÜLLER and H. UIBERALL, Confinia neurol. **1**: 312, 1938.

Schüller and Uiberall report a case of neurofibromatosis combined with a lateral spinal meningocele localized within the chest. The cystic thoracic tumor, as well as the relation of the tumor to the dural sac, was demonstrated by myelographic examination, which showed partial compression of the subarachnoid space between the levels of the sixth and the ninth thoracic vertebra and a communication between the subarachnoid space and the visible shadow in the right side of the mediastinum.

DE JONG, Ann Arbor, Mich.

Peripheral and Cranial Nerves

EFFECTS OF LIGATIONS ON NERVES OF EXTREMITIES. F. M. ALLEN, Ann. Surg. **108**:1088 (Dec.) 1938.

Allen has shown in other studies that ligations of the limbs result in an instructive form of shock and that the resistance to local asphyxia is greater than is commonly supposed, since the limbs of animals can survive complete lack of circulation for at least fifteen hours and the same is presumably true for man. Granted that a proper form of tourniquet is applied without excessive tension, the danger of gangrene under ordinary surgical conditions is largely imaginary. However, certain other sequelae are of surgical interest, particularly the occasional paralyses or contractures. Only two possible causes for such lesions exist: pressure in the zone of ligation and asphyxia. Experimental observations show that permanent paralyses arise only from direct pressure of the tourniquet and suggest that wide pressure is more injurious than a narrow band. The duration of the nerve paralyses increases in proportion to the time of ligation. The tension of the tourniquet and the temperature during ligation are important factors in the after-effects. Motor and sensory nerves differ in their sensitiveness to asphyxia in that the former suffer paralysis much more readily and also regenerate more slowly. Peripheral ganglion cells are much more resistant than the fibers of cerebral or spinal nerves.

J. A. M. A.

FANTOM LIMB PAIN: REPORT OF TEN CASES IN WHICH IT WAS TREATED BY INJECTIONS OF PROCAINE HYDROCHLORIDE NEAR THORACIC SYMPATHETIC GANGLIONS. W. K. LIVINGSTON, Arch. Surg. **37**:353 (Sept.) 1938.

In his capacity as medical examiner for the state industrial accident commission of Oregon, Livingston has examined a number of men who have had an upper extremity amputated. The proportion of these who feel pain in the fantom limb is surprisingly high, and the similarity in their complaints is so striking as to

warrant the term "fantom limb pain syndrome." Ten cases are reported. In all these the patients have had one or more injections of procaine hydrochloride near the thoracic sympathetic ganglia of the affected side. Eight patients felt immediate relief from pain, together with an extraordinary sequence of subjective and objective changes. In 4 of these the relief was of sufficient degree and duration to suggest that injection of procaine hydrochloride is of therapeutic value.

EDITOR'S ABSTRACT.

SCIATIC PAIN OF UNKNOWN ORIGIN. G. E. HAGGART, J. Bone & Joint Surg. **20**:851 (Oct.) 1938.

Haggart outlines a method of treating sciatic pain that he has employed successfully in the treatment of 75 patients with sciatica of unknown origin. The method is also applicable for immediate relief of severe sciatic pain while a clinical study is being made to determine the cause. The method is a combination of two, and in some instances three, procedures: (1) perineural injection into the sciatic nerve of a 1 per cent solution of procaine hydrochloride with 2 drops of a 1:1,000 concentration of epinephrine to the ounce (30 cc.); (2) traction to the affected extremity by the Russell method, and (3) in an increasing number of cases manipulation of the lower part of the back with the patient under anesthesia induced by intravenous injection of pentothal (sodium ethyl [1 methylbutyl] thiobarbiturate). The objective of the injection of 50 cc. of the procaine hydrochloride is to surround the sciatic nerve with the solution and possibly also to infiltrate its sheath. In addition, the fascia and substance of the piriformis muscle, and in some instances the posterior sacroiliac ligament, are thoroughly infiltrated. After injection and manipulation, with or without traction, all patients are instructed in muscular exercise of the lower part of the back and of the gluteal muscles. When the patients become ambulatory, training in posture also is given as indicated. Intensive heat and massage are likewise utilized, being chiefly applied to the lower part of the back, the region of the buttocks and the upper part of the thigh. Hot fomentations and infra-red rays have been the most effective forms of heat. Of the 75 patients, all but 10 obtained immediate relief from pain. Thirteen were benefited temporarily for from three to six months. Ten patients were free from symptoms for one year and then did not return or answer follow-up letters. In 38 cases it was eventually possible to make a definite diagnosis and so to determine the cause of the sciatica and advise appropriate treatment.

EDITOR'S ABSTRACT.

NEURONITIS OF THE CRANIAL NERVES. ALBERT T. STEEGMANN, J. Nerv. & Ment. Dis. **88**:316 (Sept.) 1938.

Steegmann reports 3 cases in which "neuronitis" affected only the cranial nerves. In the first case, a woman aged 24 experienced headache, followed by numbness of the left side of the tongue, tinnitus in the right ear and dizziness. Blurred vision and diplopia appeared later, and numbness spread to involve the whole left side of the face. Examination revealed anisocoria, blurring and hyperemia of the optic disks, nystagmus, ptosis and weakness of the internal rectus muscle on the right. The left side of the face was hypesthetic; the sense of taste was reduced on the left, and there was partial nerve deafness on the right. A cell count of the spinal fluid revealed 12 lymphocytes per cubic millimeter, and the Pandy reaction was 2 plus. Recovery was almost complete in five months. In the second case, a man aged 31, one month after recovery from sore throat and nasopharyngitis, began to have blurred vision, photophobia, dizziness and pain in the right eye. Examination revealed hyperemia of the right optic disk, bitemporal constriction of the visual fields and partial nerve deafness on the left. A month later paralysis of the left vocal cord appeared, followed by herpes labialis. The spinal fluid contained 1 lymphocyte per cubic millimeter and 37.9 mg. of total protein per hundred cubic centimeters. Recovery was complete in four months.

In the third case, retrobulbar neuritis occurred in a woman aged 28 three weeks after she recovered from an illness with headache, fever and drowsiness. The right pupils was larger than the left and reacted sluggishly to light. There was a central scotoma on the right. The spinal fluid was not examined. This case was included in the group because of the onset with fever and the occurrence of other cases of neuronitis in the vicinity. Steegmann divides the clinical course of neuronitis into three periods: onset with fever, a latent interval and a stage of paralysis.

MACKAY, Chicago.

DIPHTHERITIC POLYNEURITIS. J. M. ARENA and L. P. RASMUSSEN, J. Pediat. **13**:352 (Sept.) 1938.

Twenty-five children with diphtheria, 9 of whom had polyneuritis due to the infection, were studied. The patients were all seen late, and local as well as generalized paralysis had developed. Six of the 9 children on whose condition Arena and Rasmussen report had such mild attacks of diphtheria that they were not recognized as such and therefore were not treated. The 3 treated children received only 10,000 units of diphtheria antitoxin late in the course of the disease, 1 as late as the sixteenth day. Of the 9 children, 3 were referred to the hospital with a diagnosis of acute anterior poliomyelitis, 2 as having an abscess of the brain and 1 as suffering from Bell's palsy; the condition of the remaining 3 was diagnosed correctly. Two of the 9 children died of myocardial failure. Seven recovered in from one to four months.

EDITOR'S ABSTRACT.

RADICULAR PARALYSES OF OBSTETRIC ORIGIN AND THEIR TREATMENT. P. DUHEM, MONMIGNANT and MORO, J. de radiol. et d'électrol. **22**:531 (Nov.) 1938.

The radicular paralyses that are the subject of this paper by Duhem and his associates are generally caused either by obstetric traumatism in the course of delivery or by accidental traumatism of the shoulder and neck during life. Three types of factors are likely to cause the appearance of radicular paralyses: (1) osseous lesions on the superior extremity of the humerus, (2) lesions of the shoulder joint and (3) direct lesions of the motor nerves of the cervical region. All these lesions can be produced in the course of difficult labor with or without the application of forceps; in normal deliveries they are rare but not impossible. If a voluminous hematoma or a deformation of the epiphysial region is suspected, roentgenoscopy should be employed. Electrodiagnosis is resorted to when roentgenoscopy has demonstrated that osseous or articular lesions are absent. The diagnosis may be complicated by the fact that the lesions are multiple. Distortions or epiphysial detachments may be accompanied by vascular lesions, which may be the cause of ischemic troubles, and these in turn of secondary paralyses. In view of the complex nature of some of the lesions, it has been suggested that the general and inclusive term of "traumatisms of the shoulder of the newborn" be applied. The authors point out that the complex lesions result in the formation of perinervous and perivascular cicatricial tissues, which are the principal factors that prevent a spontaneous cure. This is why the authors utilize the solvent action of potassium iodide, which is introduced in situ by means of the galvanic current. This treatment must be employed as early as possible, particularly in case of nerve lesions, for the functional results become problematic if the nerve fibers have had time to degenerate. The authors use a 1 per cent solution of potassium iodide. The applications last thirty minutes and are made with an intensity of 4 or 5 milliamperes. The authors begin with a series of twenty treatments, the first seven or eight of which are given daily. After an interval of three or four weeks the treatments are resumed. In most cases a second and third series of treatments are necessary, and in grave conditions the treatments may have to be continued for eighteen months or two years. In answer to the question whether an excitomotor current should be applied to the paralyzed muscles, the authors say that this depends on the electrical reactions. If from the beginning no reactions of

degeneration are observed, the treatment with potassium iodide rapidly effects a cure, and the excitomotor currents may be employed to give more strength to the recuperated muscles. In case of partial degeneration it is necessary to await amelioration, because if not employed with great care the excitomotor current may be more harmful than beneficial. The authors advise against the use of the faradic current because it is too brutal. In the conclusion they stress the necessity of persistence on the part of the physical therapeutist in cases of radicular paralysis of obstetric origin.

J. A. M. A.

GLOSSOPHARYNGEAL NEURALGIA—RECURRENCE AFTER INTRACRANIAL SECTION OF THE NERVE. W. S. KEITH, Confinia neurol. **1**:345, 1938.

Keith reports the case of a woman aged 75 who complained of terrific attacks of pain just in front of the left ear. The pains were preceded by sudden twisting sensations in the left side of the throat and were brought on by swallowing. The left glossopharyngeal nerve was divided, with complete relief from symptoms. Two years later the patient again felt slight pains in the left side of the neck, and four months later a major attack occurred. The upper half of the vagus root and the nerve of Wrisberg were divided, and this was followed by complete freedom from attacks.

DE JONG, Ann Arbor, Mich.

SYMPTOMATOLOGY AND PATHOGENESIS OF LUMBOSACRAL NEURITIS. H. PETTE and P. E. BECKER, Deutsche Ztschr. f. Nervenh. **147**:1, 1938.

Pette and Becker attempt to reclassify the inflammatory diseases of the peripheral nervous system. They regard sciatica as a well circumscribed disease and prefer to call it lumbar or lumbosacral neuritis, according to the distribution of its symptoms. This study is based on a survey of 30 selected cases, 9 of which are reported in detail. In addition to the customary symptoms, which may be equivocal in some cases, the authors point out the presence of vegetative signs, such as coldness or pallor of the limb involved, hypohydrosis and edema. Objectively, they find increase of cells and protein in the lumbar spinal fluid, frequently with a pathologic mastic curve and a decreased albumin-globulin ratio. Changes in the bones or joints are not recognized as causative factors. Morphologic changes have never been reported. They believe that the etiologic factor may be a virus related to herpes zoster and that the inflammatory process is probably located in the spinal ganglia.

HOEFER, Boston.

Vegetative and Endocrine Systems

A SYNDROME OF INFANTILISM, CONGENITAL WEBBED NECK, AND CUBITUS VALGUS. HENRY H. TURNER, Endocrinology **23**:566 (Nov.) 1938.

Turner reports 7 cases of a syndrome of infantilism hitherto undescribed. The patients were all female, varying in age from 15 to 23 years. The syndrome is characterized by retardation in growth and in sexual development, deformity of the elbow (cubitus valgus) and webbing of the skin of the neck. All the patients were mentally normal and showed no deformities such as those in the Klippel-Feil syndrome. Roentgen study of the skeleton showed only demineralization and delayed union of the epiphyses. Chemical and other laboratory studies of the blood revealed no abnormalities. Treatment with a preparation of the anterior lobe of the pituitary containing the growth hormone (antuitrin-G) failed to accelerate growth. Sexual development was stimulated in 2 cases by an anterior pituitary extract containing the gonadotropic hormone.

PALMER, Philadelphia.

INFLUENCE OF AVITAMINOSES ON WEIGHTS OF ENDOCRINE GLANDS. B. SURE, Endocrinology **23**:575 (Nov.) 1938.

Sure reports the results of various vitamin deficiencies on the weights of the pancreas, adrenals, thymus, thyroid and pituitary. The final weights of the endocrine glands expressed as percentages of the body weight were used as the standard. Increase and decrease in weights of the endocrine glands of the test animals expressed in percentages of the body weight as compared with the weights for the control animals, restricted to the same plane of nutrition, are referred to as "hypertrophy" and "atrophy," respectively. The test period was from thirty-five to forty days. In 60 groups of animals with vitamin A deficiency there was observed hypertrophy of the pancreas, amounting to 40 per cent. In animals with vitamin B_1 deficiency there was marked hypertrophy of the thyroid and adrenal glands. The most noteworthy change in weight of the endocrine glands associated with avitaminoses was the marked atrophy of the thymus in vitamin B_1 deficiency, which occurred in 100 per cent of the pathologic animals. The atrophy was correlated with histologic changes. Hypertrophy of the pituitary gland was observed in cases of vitamin B_1 and B_2 deficiency to the extent of 40 and 25 per cent respectively. Repeated depletion and replacement of vitamin B_1 were undertaken in a significant group of animals over a period of from six to ten months. Comparison with animals suffering from a single depletion revealed that the hypertrophy of the pituitary gland entirely disappeared in the first group, that of the thyroid gland was reduced to insignificant proportions, and that of the adrenals was reduced from 50 to 20 per cent. All these figures are relative to fluctuations in body weight. In other words, it takes repeated bombardments with severe depletions before the extent of loss in weight of these endocrine glands begins to approximate that of the body as a whole.

PALMER, Philadelphia.

THE HYALINE CHANGE IN THE BASOPHIL CELLS OF THE PITUITARY BODY NOT ASSOCIATED WITH BASOPHILISM. ARTHUR D. ECKER, Endocrinology **23**:609 (Nov.) 1938.

The basophilic cells in the anterior lobe of a series of 721 pituitary glands removed routinely at necropsy were examined carefully by Ecker for the hyaline change which heretofore has been considered the sole common anatomic denominator in cases in which the clinical syndrome of pituitary basophilism is present. Fifty-four of the pituitary glands contained basophilic adenomas. The hyaline change was present to a marked extent in 8 of the 54 cases, an incidence of 1.1 per cent. However, the clinical and postmortem records revealed no evidence of the basophilic syndrome, even though in 1 case a basophilic adenoma also was present. The cells of the 54 basophilic adenomas in this series, as well as those of 18 others, were examined, and the hyaline change was observed in 4 cases (5.5 per cent). However, in these cases there was neither hyalinization of the basophilic cells outside the adenomas nor evidence of Cushing's syndrome in the clinical and postmortem records. It appears, therefore, unwarranted to consider hyalinization or degranulation of the basophilic cells in the anterior lobe of the pituitary gland of man as invariably associated with the state designated as pituitary basophilism.

PALMER, Philadelphia.

SUBCLINICAL ADRENOGENITAL SYNDROME. S. J. GLASS and H. C. BERGMAN, Endocrinology **23**:625 (Nov.) 1938.

Glass and Bergman report quantitative determinations of androgen and estrogen in 30 persons (28 women and 2 men) manifesting varying degrees of a benign adrenogenital syndrome. In the women the complaints were hirsutism, obesity and ovarian dysfunction. Libido and fertility were greatly affected. Depression and anxiety states were common. Twenty women dated the onset of the disorder from puberty or soon after, and 7, from a pregnancy. The 2 men presented gynecomastia, loss of libido and impotence, together with genital atrophy. Roentgen

studies failed to reveal tumors of the adrenal gland. The majority of the women excreted much higher amounts of androgen than normal, and occasionally higher quantities of estrogen. The 2 men excreted greater quantities of estrogen than normal. In other words, benign sex reversal states apparently are associated with a reversal of the normal ratio of estrogen to androgen. Urinary androgen and estrogen are in far greater concentration in the malignant than in the benign types of adrenogenital syndrome, thus differentiating the surgical from the nonsurgical forms. The authors suggest assays of estrogen and androgen and roentgen studies instead of surgical exploration as diagnostic measures.

PALMER, Philadelphia.

POLYGLOBULISM PROVOKED BY EXTRACTS OF ANTERIOR LOBE OF HYPOPHYSIS AS PROOF OF EXISTENCE OF A HEMOPOIETIC HORMONE. J. FLAKS, I. HIMMEL and A. ZOTNIK, Presse méd. **46**:1506 (Oct. 12) 1938.

Flaks and his associates state that clinical and experimental observations cited in a previous report indicated that, under physiologic conditions, the hypophysis regulates hemopoiesis. They attempted to prove that this hemopoietic action of the hypophysis depends on a hormone which differs from the hormones already known. In order to prove the existence of a special hemopoietic hormone, they made investigations in two directions: (1) by ascertaining the atrophy of the hemopoietic tissue of bone marrow and of the morphogenic elements of the blood following the ablation of the hypophysis, and their reactivation by the administration of hypophysial substance; (2) by provoking hemopoietic hyperactivity through surcharging the normal organism with supposedly hemopoietic elements. The experiments were made on rats. Observations on the variations in the blood elements in normal rats show that the number of erythrocytes never exceeds 9,500,000. Consequently, the authors consider that polyglobulism is indicated by values for erythrocytes which exceed 10,000,000. Polyglobulism is the test for the demonstration of the hemopoietic hormone. Hypophysial substance was administered to hypophysectomized as well as to normal rats. On the basis of these and of earlier experiments, the authors reach the conclusion that it is justifiable to admit the existence of a hemopoietic hormone in the hypophysis.

EDITOR'S ABSTRACT.

HYPOPHYSIAL DIABETES: ACTION OF FEVER. H. ZONDEK and A. KAATZ, Presse méd. **46**:1835 (Dec. 14) 1938.

Zondek and Kaatz describe 2 cases of hypophysial diabetes. The first was that of a woman aged 32 who presented hypophysial symptoms; the second, that of a man aged 30 who had a hypophysial tumor and symptoms of hypophysial dissociation complicated by latent diabetes. In both cases the diabetes was cured after an attack of fever, in the woman after an attack of angina and in the man after a fever that was provoked by the intravenous injection of antityphoid vaccine. In both cases the diabetes was of the hypophysial type; the fever must have inhibited a diabetogenic principle. Whereas fever produces ordinarily an aggravation of pancreatic diabetes, it may have the opposite effect in certain cases of hypophysial diabetes. The authors are inclined to believe that the principle inhibited by the fever is not the diabetogenic hormone described by Houssay but rather that which acts through the medium of the adrenal cortex. The diabetes in these cases results in exaggerated transformation of nonhydrocarbonaceous substances into carbohydrates in accordance with von Noorden's theory of diabetes, but it is possible that besides this factor there are others that intervene—factors which inhibit either the fixation of glycogen or the oxidation of sugar. Thus, the modern ideas of the nature of diabetes approach more and more the conception that it represents a complex disturbance of the interglandular regulation, as is the case in other endocrine disorders, such as exophthalmic goiter.

J. A. M. A.

Cerebrospinal Fluid

VITAMIN C IN THE SPINAL FLUID. HERMAN WORTIS, JAMES LIEBMANN and S. BERNARD WORTIS, Am. J. M. Sc. **196**:384 (Sept.) 1938.

The authors made determinations of vitamin C in the blood and spinal fluid of 257 patients. The lower limit of the normal vitamin C content of the blood plasma was found to be 0.7 mg. per hundred cubic centimeters. The lower limit of the normal ascorbic acid content of the spinal fluid was considered to be 1.82 mg. per hundred cubic centimeters. A normal ascorbic acid value (above 0.7 mg.) and a very low value (below 0.4 mg.) for the blood were almost invariably associated with correspondingly normal and subnormal values for the spinal fluid. In the intermediate subnormal range (vitamin C level of from 0.4 to 0.69 mg.) no such close correlation existed. There was no significant age correlation in the level of vitamin C in the blood or spinal fluid. Probably vitamin C plays a role in metabolism of the nerve tissue, although the mechanism of the action is not as yet determined.

MICHAELS, Boston.

THE ORIGIN OF THE FALL IN THE PRESSURE OF THE CEREBROSPINAL FLUID AFTER ITS ARTIFICIAL ELEVATION BY JUGULAR OCCLUSION. T. H. B. BEDFORD, Brain **61**:62, 1938.

The effect of jugular occlusion on the cerebrospinal fluid pressure in the cisterna magna and on the venous pressure in the torcular have been described in earlier papers by Bedford. It was found that the rise in the pressure of the cerebrospinal fluid which follows sudden occlusion of the external jugular veins is a temporary phenomenon and that the pressure usually returns to about the original level within the space of one hour. The venous pressure in the torcular was also observed to decrease; the fall, however, was not as rapid or as complete as that in the pressure of the cerebrospinal fluid, and at the end of the experiment the torcular venous pressure was sometimes more than twice its original height. These pressure changes occurred independent of variation in the system arterial pressure. It was concluded that the fall in pressure of the cerebrospinal fluid is due mainly to the establishment of collateral venous circulation. It was considered, however, that there had been also a reduction in the total volume of the cerebrospinal fluid. In the present investigation, Bedford attempted to study the problem by observing the effect of jugular occlusion on the rate of absorption of isotonic solution from the subarachnoid space. A manometer in the cisterna magna was connected by a three way tap with a device by which the pressure of the cerebrospinal fluid could be maintained at any desired level and the rate of inflow or outflow of fluid from the subarachnoid space be determined. The apparatus employed for this purpose was modeled on that used by Mortensen and Weed in their study of the absorption of isotonic solution from the subarachnoid space. As a result of these experiments, Bedford concludes that the return of the pressure of the cerebrospinal fluid to normal after jugular occlusion is due to a diminution in the volume of the cerebrospinal fluid; this diminution may be brought about by increased absorption in the parts of the subarachnoid space which are least influenced by the raised venous pressure; the accompanying fall in the venous pressure in the torcular is mainly dependent on the fall in the pressure of the cerebrospinal fluid.

SALL, Philadelphia.

SUGAR CONTENT OF THE CEREBROSPINAL FLUID AND ITS RELATION TO BLOOD SUGAR IN HEALTHY PERSONS AND IN PATIENTS. A. VON BOTHMER, Ztschr. f. klin. Med. **134**:754 (Sept. 15) 1938.

The normal range of the sugar content of the cerebrospinal fluid and the normal ratio between the sugar content of the cerebrospinal fluid and that of the blood were determined for 105 healthy persons. To determine the conditions in pathologic processes, 378 examinations were made simultaneously on the cerebrospinal fluid and the blood of patients with various diseases. In his studies on normal persons

the author found that as the sugar content of the blood increases the sugar content of the cerebrospinal fluid also shows a tendency to increase; that is, it is impossible to speak of a normal range of the cerebrospinal fluid sugar which is independent of the blood sugar. However, the ratio between the sugar content of the cerebrospinal fluid and that of the blood is not constant. It is higher in cases in which the blood sugar values are low than in those in which they are high. The author's observations on the ratio between the sugar content of cerebrospinal fluid and that of blood differ from those of some other investigators. His opinion of the sliding adjustment of the normal ranges suggests that the active secretory function of the ependyma of the plexus has a tendency to aim at a "normal" height for the sugar content of the cerebrospinal fluid. This secretory function is strong when the blood sugar is low and weak when the blood sugar is high. However, the secretory activity is counteracted by physicochemical forces, which apparently are responsible for the fact that even in case of an increased blood sugar content the ratio between the sugar content of the cerebrospinal fluid and that of the blood does not fall below a certain absolute value. The author's studies on patients with pathologic conditions revealed that the determination of the ratio is of greater diagnostic significance than that of the absolute sugar content of the cerebrospinal fluid. Reductions in the ratio occur in association with tuberculous meningitis, purulent meningitis, influenzal meningitis and syphilitic meningitis. Increases in the ratio are not specific for certain diseases and consequently are of slight value for differential diagnosis; their diagnostic value lies in the fact that they usually indicate a diffuse and severe cerebral lesion.

EDITOR'S ABSTRACT.

Treatment, Neurosurgery

INSULIN THERAPY IN MENTAL DISEASE. D. V. CONWELL and C. J. KURTH, Endocrinology **23**:767 (Dec.) 1938.

Conwell and Kurth report results and observations in the insulin shock treatment of 37 schizophrenic, 9 manic-depressive, 6 involutional melancholic and 2 psychasthenic patients. They conclude that insulin shock therapy is of definite value in the treatment of schizophrenia. It was helpful in the paranoid, simple, hebephrenic and catatonic types, in the order named. It was of equal value in the treatment of patients in the manic phase of manic-depressive psychosis and was effective in the 2 cases of psychasthenia. Its value was questionable in the depressed phase of manic-depressive psychosis and in involutional melancholia. The character of the preliminary sugar curves or the fasting blood sugar levels was of no value in predicting the results. The blood sugar determinations were of definite value in pretreatment consideration, and of great value in the management of the therapy. The authors believe that part of the danger encountered in insulin shock therapy can be controlled by means of a low carbohydrate diet, the need of larger doses of insulin being thus avoided. They could observe no immediate or late changes in the function of the parathyroid or pituitary gland. Hypofunction of the pancreas was transitory. The therapy seemed to cause early, and in some patients prolonged, adrenal hyperfunction or hypofunction, of a minor character. There was a tendency toward modified gonadal function. It frequently caused early and persistent decrease in the function of the thyroid gland, sufficient to require thyroid therapy in 8 cases. Thyrotoxicosis was decreased in 9 patients. There was no evidence of permanent visceral damage. The therapy caused major changes in the central and peripheral nervous systems in 3 patients. In 1 of these the damage may be permanent. There were no deaths.

PALMER, Philadelphia.

TREATMENT OF NEUROGENIC MEGACOLON WITH SELECTIVE DRUGS. W. O. KLINGMAN, J. Pediat. **13**:805 (Dec.) 1938.

Klingman believes that, clinically, idiopathic or acquired megacolon falls into one of two groups: rectosigmoid achalasia, in which one finds a failure of the

rectosigmoid apparatus to relax, and the group in which the motor function of the parasympathetic system fails to act effectively above the rectosigmoid region. Rectosigmoid achalasia may arise from two causes: overactivity of the sympathetic system resulting in spasm of the rectosigmoid apparatus and failure of the parasympathetic system to inhibit properly the rectosigmoid apparatus. Drugs acting exclusively as paralyzers on the parasympathetic system are beneficial in establishing better emptying of the intestine in certain cases of megacolon. The drug of choice to inhibit liberation of acetylcholine should be atropine, but its highly toxic effects contraindicate its administration. A less toxic atropine-like compound, syntropan (the phosphate of the tropic acid ester of 3-dimethylamino-2, 2-dimethyl-1-propanol) was selected because it controls tonus without interfering with the peristaltic reflex. Clinically the two types of rectosigmoid achalasia cannot be distinguished except after trial of appropriate drug therapy, but through the use of barium sulfate enemas it is frequently possible to demonstrate whether or not there is rectosigmoid spasm with or without delayed emptying of the colon. In cases of rectosigmoid achalasia there is marked delay in emptying, whereas in the cases in which there is deficient motor function on the part of the parasympathetic fibers to the colon above the rectosigmoid apparatus there is good emptying of the lower part of the colon but retention of the barium sulfate in the upper part. On the basis of this classification, the author proposes a selective form of treatment for each of the conditions classified. When roentgen interpretation makes it possible to establish that the rectosigmoid apparatus is functioning, prostigmine should be tried. If the rectosigmoid apparatus is not functioning, first sulfate benzedrine and then syntropan should be tried. If there is no response to either of the latter drugs, lumbar ganglionectomy and presacral resection are proposed, until a more satisfactory selective drug can be found. J. A. M. A.

INFLUENCE OF INSULIN TREATMENT UPON SCHIZOID PERSONALITY TRAITS. H. FELDMAN, R. P. FIERO and R. C. HUNT, Psychiatric Quart. **12**:710 (Oct.) 1938.

The authors report on personality changes produced in 3 schizophrenic patients of the paranoid type after insulin shock treatment. The 3 cases showed many points of similarity. The patients were all men; all were married, and all were close to the fourth decade of life. All showed definitely introverted prepsychotic personality traits with gradual shading into schizophrenic reactions and, finally, an outspoken schizophrenic psychosis. The content of the psychosis also displayed many similarities. In the first case there were 32 treatments, 12 of which produced coma; in the second case, 24 treatments, in 19 of which there was coma, and in the third case, 13 treatment, in 5 of which there was coma. None of the patients had convulsions. After treatment all displayed personality changes of marked character, resulting in shift from an introverted, asocial, withdrawing makeup to that of an overt, social and well balanced personality. In two of the cases the improvement was of short duration. In 1 case of relapse the psychosis was remarkable in that it appeared to be an extroverted, hypomanic disorder, which contrasted strongly with the previous schizophrenic reaction. In the third case the sociable extroverted, well balanced attitude continued after the end of one year.

PALMER, Philadelphia.

CARDIAC ACCIDENTS ASSOCIATED WITH CARDIAZOL CONVULSION THERAPY. W. MCADAM, Glasgow M. J. **12**:221 (Nov.) 1938.

While treating 16 patients suffering from schizophrenia with injections of metrazol, McAdam discovered that in 1 a well marked reduplication of the second mitral sound and in 2 auricular fibrillation developed. None of these patients had shown any clinical cardiac abnormality before commencing treatment, though in 1 instance preponderance of the right side of the heart was revealed by the electrocardiogram. The abnormal cardiac conditions were of short duration, cleared up without treatment and left no sign of myocardial damage. In contrast to these

3 cases, a mentally defective boy of 19, showing the signs of schizophrenia simplex, and of poor physique, with a pigeon-shaped chest, right ventricular preponderance and a history of repeated asthmatic attacks during the last five years, received injections of metrazol thrice weekly after the cessation of his asthmatic attacks, and there was at no time any sign of arrhythmia or other cardiac disability.

J. A. M. A.

DANGERS AND EMERGENCIES OF INSULIN THERAPY OF THE PSYCHOSES. L. A. FINIEFS, J. Ment. Sc. **84**:678 (Sept.) 1938.

The danger during insulin therapy of the psychoses is negligible and the occurrence of serious emergencies infrequent. On 4,379 patient insulin days, 3,205 comas were induced, and only 6 serious emergencies arose. No fatality occurred. With more careful selection of patients in order to exclude the physically unfit and with greater experience, this low incidence of emergencies may be reduced even further.

KASANIN, Chicago.

CARDIAZOL TREATMENT OF SCHIZOPHRENIA. ARTHUR HARRIS, J. Ment. Sc. **84**:735 (Sept.) 1938.

Harris compared 100 cases in which metrazol treatment was used with 100 cases used as controls. He found it difficult to estimate the results, since there was a great deal of variation in the degree and kind of recovery. Only 24 patients showed no improvement, either temporary or permanent, during the course of treatment with metrazol. Patients whose illness had lasted less than twelve months showed a much better rate of remissions than those whose illness had lasted more than a year. Of the 106 patients in the control group, 35 made a satisfactory recovery, and 71 did not, giving a recovery rate of 33 per cent.

The difference in the rate of discharge between the treated and the untreated patients did not appear to be sufficiently great to be conclusive or significant, especially since the treatment was not given to every patient admitted with schizophrenia and a certain amount of selection was therefore exercised. It must be remembered, however, that in the control group the recoveries were spread over a much longer period than in the group of treated patients, so that the onset of the remission appears to have been hastened, if not actually induced, in the latter group. The superiority of the results in patients with previous remissions is striking, and it appears probable that there exists a disease in the schizophrenic group which is liable to remission and relapse and is particularly benefited by convulsive treatment, the psychotic periods being shortened and the onset of the remissions hastened.

The general impression gained is that this treatment exercises no profound effect on the course of the disease, but that it may hasten recovery in cases in which remissions develop, and may arrest the progress of the disease and prevent its worst ravages in cases in which they do not develop. In this, it is probably no more effective than other types of shock treatment, such as artificial pyrexia and insulin, but it compares favorably with them as regards ease of administration and freedom from danger.

KASANIN, Chicago.

STOMATITIS OF VITAMIN-B_2 DEFICIENCY TREATED WITH NICOTINIC ACID. PHILIP MANSON-BAHR and O. N. RANSFORD, Lancet **2**:426 (Aug. 20) 1938.

The authors report beneficial results with nicotinic acid in a woman aged 62 who for five years had had morning diarrhea. Stomatitis and glossitis appeared promptly after the onset, followed in eighteen months by paresthesias in one leg. She was twice admitted to a hospital for a gastric ulcer; subsequently, a diagnosis of sprue was made. Eventually, she was placed on a full diet with an alkaline mixture and was given 150 mg. of nicotinic acid daily. In ten days she was discharged from the hospital. Intolerance to the drug was discovered after ten days of administration; the dose was then reduced to 50 mg. daily. The toxic effects

continued. These consisted of stinging pain at the angles of the jaw, radiating to the ears, faintness and flushing of the face. This was followed by an "urticarial rash" on the chest, arms and thigh, which disappeared without treatment.

KRINSKY, Boston.

BULGARIAN TREATMENT OF POST-ENCEPHALITIC PARKINSONISM: COMPARISON WITH ENGLISH BELLADONNA. D. HILL, Lancet **2**:1048 (Nov. 5) 1938.

Hill treated 14 patients suffering from postencephalitic parkinsonism with a decoction of Bulgarian belladonna. Improvement followed in 10 patients, who showed decreased rigidity; of these, 4 also showed diminished tremor. The oculogyric crises were not much improved. Ten patients also gained weight. When a decoction of English belladonna in wine and later one in acid alcohol were substituted, the improvement in the parkinsonism was maintained. The patients did not at first notice the substitution. With the acid alcohol decoction, signs of belladonna poisoning became pronounced in 6 patients; this may have been because this preparation contains more alkaloids of belladonna than does the wine decoction. The therapeutic properties of Bulgarian belladonna do not seem to differ from those of its English equivalent.

J. A. M. A.

TREATMENT OF SCHIZOPHRENIA WITH INSULIN AND METRAZOL. K. BLUMENTHAL, Harefuah M. J. **15**:173 (Oct.) 1938.

Blumenthal treated 50 patients with schizophrenia with combined insulin and metrazol therapy during a period of eleven months. Twenty-four patients recovered; 11 improved. Seventy per cent of the patients were benefited by the treatment. Eighty-five per cent of the patients with an illness of less than three years' duration responded to the treatment. Only 33 per cent of the patients reacted favorably when the disease was of over three years' duration. Patients who showed good insight into their illness were considered recovered and were regarded as only improved when such insight did not exist. There were only 3 cases of recurrence during a period of observation of eleven months. In 1 case coma persisted for two days. In another case auricular fibrillation appeared for five hours; treatment was successfully continued in this case despite the arrhythmia. A patient who was treated successfully with twenty-eight injections died suddenly six weeks after his discharge. Two cases of fracture during the course of metrazol treatment are recorded. In 1 of them the humerus and femur were fractured at the same time. While no rule can be given as to the number of injections indicated in a given case, the author mentions thirty-five as a minimum.

SAVITSKY, New York.

TREATMENT OF DANGEROUS SEXUAL ANOMALIES BY CASTRATION. J. LEY, J. belge de neurol. et de psychiat. **38**:344 (May) 1938.

Ley discusses the use of castration in the treatment of sexual disorders and reports a case of exhibitionism in which the patient was treated and cured by this procedure. Libido and potentia disappear more or less rapidly after castration in the adult. The physical sequelae depend on the age at the time of castration. An increase in body weight is frequent but not constant, and there is usually some degree of gynecomastia. Muscular power is usually diminished. The voice is usually not changed; there is a slight loss of body hair. The true eunuchoid habitus appears rarely. The mental residuals vary, depending on the psychologic differences in the individual person, the patient's attitude toward the operation and the age at the time of the operation. There is sometimes a certain amount of depression. The sexual changes in women are similar to those in men. Ley concludes that castration is indicated in cases of sexual anomalies and that in certain instances it is the best type of treatment available. However, the operation should be preceded by long and detailed psychotherapeutic preparation. Castration should be

proposed only if other types of therapy have been ineffective. In general, it should not be carried out before the age of 25, especially not during the age of puberty. When sexual anomalies accompany schizophrenia or marked schizoid tendencies castration is contraindicated, for experience has shown that it has little effect in such cases. The danger of self castration is perhaps the only indication.

DE JONG, Ann Arbor, Mich.

USE OF METRAZOL IN RELIEVING THE PERIODIC AGITATION OF EPILEPTIC PATIENTS. A. LEROY, J. belge de neurol. et de psychiat. **39**:373 (May) 1938.

Leroy demonstrated the beneficial influence of the intravenous injection of 0.6 Gm. of metrazol on the agitated phase following the convulsive seizure in an epileptic patient; he believes that the drug has a specific quieting effect in such cases. He states that metrazol, which has already been used with success in the treatment of many mental diseases such as schizophrenia and melancholia, is also of value in the treatment of epileptic patients. DE JONG, Ann Arbor, Mich.

INTRACRANIAL ANEURYSM: A SURGICAL PROBLEM. W. J. GERMAN, Confinia neurol. **1**:344, 1938.

German reports 6 cases of bleeding intracranial aneurysms in which a surgical attack was considered. Excision of a posterior cerebral aneurysm in 1 case resulted in recovery. Of the 5 patients not operated on, 2 died. Ventriculography revealed hydrocephalus in 2 instances and porencephaly in 1.

DE JONG, Ann Arbor, Mich.

DECREASE OF MUSCULAR EFFICIENCY IN MYASTHENIA GRAVIS. WALTER BIRKMAYER, Deutsche Ztschr. f. Nervenh. **147**:118, 1938.

Birkmayer studied 3 patients with myasthenia gravis, particularly with regard to the effect of fatigue. Quantitative tests showed that after fatigue there is no increase of performance with renewed intention, such as normal persons present. Moving pictures of the myasthenic gait show that the duration of standing between steps is considerably prolonged as compared with the time of actual motion of the legs. The figures for normal persons are 49:51; those for myasthenic patients, 70:30. While prostigmine increases the muscular strength and endurance, it does not change the peculiar patterns of muscular performance. HOEFER, Boston.

NEW POINTS OF VIEW IN EVALUATING INSULIN SHOCK THERAPY OF SCHIZOPHRENIA: A COMPARATIVE STUDY OF 200 PATIENTS TREATED BY ORDINARY METHODS. G. LANGFELDT, Monatschr. f. Psychiat. u. Neurol. **98**:351 (Aug.) 1938.

A scrutiny of the results of insulin shock therapy of schizophrenia discloses great variations in the percentage of remissions reported by different writers. In an attempt to explain these variations, Langfeldt investigated 100 cases of schizophrenia in which the symptoms clearly pointed to an endogenous form of the disorder and an equal number in which atypical symptoms were noted. In the first group, spontaneous remissions or improvement was observed in 23.3 per cent of the patients who had been ill for less than six months. The corresponding figure for the patients with atypical symptoms was 60 per cent. In a review of all the cases belonging to the second group from six to ten years later it was found that recovery had occurred in 32 per cent and marked improvement in 35 per cent. On the other hand, only 3 per cent of the patients with typical symptoms had shown permanent remissions after a similar period. Langfeldt believes that variable results were obtained with insulin shock therapy because atypical and endogenous forms of schizophrenia were represented in varying proportions in the different groups treated. The atypical form exhibits a strong

tendency to spontaneous healing, which is probably accelerated by the use of insulin. It is doubtful whether insulin therapy is of benefit in the endogenous form, but before a final conclusion can be reached, more careful clinical studies than those hitherto recorded are needed. ROTHSCHILD, Foxborough, Mass.

THERAPY OF ENCEPHALITIS AND OF RELATED NEUROTROPIC INFECTIONS OF NERVOUS SYSTEM. W. M. VAN DER SCHEER and R. ZIJLSTRA, Nederl. tijdschr. v. geneesk. **82**:4666 (Sept. 24) 1938.

Van der Scheer and Zijlstra direct attention to the use of methenamine in the treatment of encephalitis and of related neurotropic infections. They report the results obtained with it in more than 200 cases. A tabular report indicates that the material included patients with various forms of encephalitis, disseminated and transverse myelitis, postencephalitis parkinsonism, chorea minor, herpes zoster, radiculitis, Landry's paralysis, polyneuritis, poliomyelitis. On the basis of their experiences, the authors recommend this treatment. They administer methenamine in the form of a 40 per cent solution by means of intravenous injections. The individual dose is 10 cc., which usually is given every other day. The total dose is from 100 to 200 cc. J. A. M. A.

Muscular System

A CASE OF TRANSITION BETWEEN CHARCOT-MARIE-TOOTH AND GENERAL FORM OF PROGRESSIVE SPINAL MUSCULAR ATROPHY. SAMUEL D. INGHAM, Bull. Los Angeles Neurol. Soc. **3**:136 (Sept.) 1938.

Ingham records the case of a woman aged 30 who had had pes cavus and hammer toes on both sides since childhood and who since the age of 27 had had rapid contracture of the right Achilles tendon, which was not improved by tenotomy. The maternal grandmother, aged 85, had contracted feet and had been unable to move the lower extremities for twenty years. Her seven children, including the patient's mother, had similar feet. Examination revealed marked pes cavus and hammer toes on both sides, with some atrophy of the right calf and possibly of the thenar eminences. No paralysis or fibrillary twitchings were present, and there was no sensory impairment. The tendon reflexes were normal except for slight exaggeration of the right knee and ankle jerks. Babinski and Chaddock signs were present bilaterally, but the Gordon, Oppenheim and Rossolimo signs were not obtained. The abdominal reflexes were present. Ingham believes that the clear evidence of involvement of the pyramidal tracts places the condition in an intermediate position between the Charcot-Marie-Tooth and the spinal type of progressive muscular atrophy. MACKAY, Chicago.

PROSTIGMINE TEST IN MYASTHENIA GRAVIS. R. S. SCHWAB and H. R. VIETS, New England J. Med. **219**:226 (Aug. 18) 1938.

In clinic and office practice the long period of observation formerly used by Schwab and Viets is both unpractical and unnecessary. They therefore modified the prostigmine test so that it can be completed in one hour. The best objective symptom for evidence of improvement is determined; for example, the degree of ptosis, the ability in swallowing or talking or the muscular strength as measured by the ergograph or dynamometer. Three cubic centimeters of prostigmine, to which 0.01 grain (0.6 mg.) of atropine sulfate has been added, is injected intramuscularly. Thereafter, at intervals of ten minutes for an hour, the degree of objective improvement is noted in one column, with grading as follows: 0, no improvement; 1, slight improvement; 2, moderate improvement; 3, considerable improvement, and 4, complete recovery or marked improvement. In a second column, with the same grading, the patient's subjective opinion of the improvement is scored. The figures in the two columns are added, and the total score

is obtained. The maximal score is 48. If the total value is less than 8, the result of the test is negative, and it is extremely unlikely that the patient has myasthenia gravis. If the total value is from 8 to 18, the outcome of the test is doubtful and it should be repeated, or a therapeutic trial with oral administration of prostigmine should be made. If the score is more than 17 (from 18 to 48), the result of the test is positive. This is presumptive evidence of the diagnosis of myasthenia gravis. In general, the two columns are similar and parallel each other to a striking degree. The test has been used in 35 cases of myasthenia gravis, with a score of 25 or more. No patient with myasthenia gravis gave a negative result. In 10 cases the tests were repeated with practically no change in the scores. Owing to the marked change in symptoms of patients with myasthenia gravis after an injection of prostigmine, some observers believe that making several observations is unnecessary for scoring. This is true, perhaps, in three fourths of the patients with myasthenia, but in the nonmyasthenic group, particularly those with the chronic form, suggestion plays a large part, and they may score high enough on the subjective symptoms to make the diagnosis of myasthenia possible unless several tests are made. In patients with diseases that simulate myasthenia gravis, negative prostigmine reactions were obtained.

EDITOR'S ABSTRACT.

MYOCLONIC SYNDROME IN A CASE OF AMYOTROPHIC LATERAL SCLEROSIS. G. DÖRING, Deutsche Ztschr. f. Nervenh. **147**:26, 1938.

Cases of myoclonia have rarely been reported in association with amyotrophic lateral sclerosis. Döring reports a case in which myoclonus and atrophies were the only clinical signs. The myoclonic twitchings were generalized, with a frequency of from 100 to 200 per minute. Histologic examination revealed bilateral demyelination of the pyramidal tracts and foci of spotty degeneration in the white matter of the cerebellum, around the dentate nuclei. Döring regards the myoclonia as a disturbance in the regulatory mechanism of the olivocerebellar system.

HOEFER, Boston.

PROGRESSIVE MUSCULAR DYSTROPHY. R. STÄHLI, Schweiz. med. Wchnschr. **68**: 1226 (Nov. 5) 1938.

Stähli states that occasionally there are cases of muscular dystrophy in which the values for creatine and creatinine in the serum and urine are normal. A case of this type was observed by the author. A man at the age of 51 sustained a trauma of the vertebral column, and later atrophic and hypertrophic processes in the muscles developed. In its external aspects the condition corresponded to the type to which Griesinger applied the term pseudohypertrophic myopathy, which occurs not only during childhood and in familial groups but also in later life and without demonstrable hereditary tendency. The relation between myopathy and trauma is probably of a different nature in the case reported than in the cases described by Ken Kuré and others. The creatine and creatinine metabolism was found to be within normal limits, but it cannot be doubted that this man had severe, progressive myopathy. This case and a description by Curschmann indicate that anomalies in the creatine metabolism present a frequent, but only a facultative, symptom of myopathy. Recently it has been pointed out again by Netrolitzky and Pichler that disturbances in the creatine metabolism and the clinical behavior of muscular dystrophy do not parallel each other. These authors observed clinical improvements after malaria therapy and in case of unchanged levels of creatinuria. On the other hand, they report that there was retrogression in the degree of creatinuria under the influence of aminoacetic acid without simultaneous increase in muscular strength.

J. A. M. A.

PROGRESSIVE MUSCULAR DYSTROPHY IN ROVING NORWEGIAN FAMILY. K. WAGNER, Norsk mag. f. lægevidensk. **99**:1087 (Oct.) 1938.

Wagner examined 14 affected members of the roving family in question, spread over the western part of Norway. There was paralysis without rigidity; of the patients with advanced atrophy, accompanied by suspended or weakened tendon reflexes, only 3 or 4 were so disabled that they had to be quiet. Of the 35 marriages that he traced in the family, 12, or about 35 per cent, were intermarriages, which he explains as due to social isolation. He concludes that a partially dominant factor is present, the affected persons being heterozygote with reference to the factor. The fact that 3 women, although undoubted bearers, have escaped the disorder may be accidental, but may also mean that women are less liable to it than men. While the probability is not strong, he says, that nervous disorders are correlated with the muscular dystrophy, he found deaf-mutism in 2 cases in this family, epilepsy in 1, manic-depressive insanity in 1, mental unbalance in 2, "queerness" in 1 and schizophrenia in 1. There was also a criminal trend.

J. A. M. A.

Special Senses

EFFECTS OF OXYGEN DEPRIVATION ON THE CENTRAL VISUAL FIELD. J. N. EVANS and R. A. MCFARLAND, Am. J. Ophth. **21**:968 (Sept.) 1938.

Evans and McFarland conclude from 36 experiments on 8 eyes of 4 subjects under conditions of oxygen deprivation that (1) central visual acuity remained unaffected, even at the peak of oxygen deprivation; (2) the angioscotoma widened progressively with progressive oxygen deprivation until it obliterated the visual field, except for a region of from 8 to 10 degrees about the macula; (3) there seemed to be no relation between the minor changes occurring in the blood pressure and the angioscotoma, and (4) there was a marked variation in the extent and rate of widening of the angioscotoma, not only between individual persons but also, to a lesser degree, in one eye as compared with the other eye of the same person. By placing a patient under the stress of oxygen deprivation, latent defects in the retina may become apparent. In numerous conditions associated with venous stasis, widening defects of the angioscotoma identical in form and extent with those created in the present experiments have been eradicated by the administration of drugs—ephedrine sulfate—which cause vasoconstriction and a rise of blood pressure. Similar medication might be used to overcome the visual and cerebral effects of anoxia in aviators.

EDITOR'S ABSTRACT.

ON NORMAL DISCS IN PATIENTS WITH CHIASMAL LESIONS. A. A. MCCONNELL and A. J. MOONEY, Brain **61**:37, 1938.

In the majority of cases of pituitary tumor the optic disks are pale, but in a certain number the disks are of normal appearance. The report by an ophthalmologist of a normal disk in a patient with gross field defects and an established tumor in the region of the chiasm has been questioned by some surgeons, who have doubted the accuracy of the observation. The present study is based on 6 cases of tumor involving the chiasm in which the disks were normal. Postmortem observations were made in 4 cases. The visual field changes noted were: bitemporal hemianopia in 3 cases, almost complete blindness in 1 case, bilateral central scotoma in 1 case and left homonymous hemianopia in 1 case. In 5 of the 6 cases the tumor was retrochiasmal; in the sixth case it was prechiasmal, but differed from the usual type of a tumor in this position in its failure to displace the optic nerves laterally. In each case the optic nerves were normal in appearance and ran straight from the optic foramens to the chiasm.

In another series of 8 cases in which there were similarly definite symptoms and signs of tumor in the same situation, primary atrophy of the optic nerve was present. In this group of cases of primary optic atrophy all the tumors were

prechiasmal; the optic nerves appeared to be whiter than normal, and they were flattened and curved around the tumor.

The authors conclude that pallor of the optic disks in cases of tumor in the region of the chiasm is related to displacement or stretching of the optic nerves and that the nerves are more likely to be free from embarrassment when the tumor lies behind than when it lies in front of the chiasm. In the authors' experience, meningiomas which grow from the tuberculum sellae are constantly associated with pallor of the disks.

The difference in operative mortality between the two groups is marked. In the first group in which the disks were normal, 4 of 6 patients died. In the group of prechiasmal tumors associated with primary optic atrophy 1 of 8 patients died.

SALL, Philadelphia.

VERTIGO: ITS NEUROLOGICAL, OTOLOGICAL, CIRCULATORY, AND SURGICAL ASPECTS. W. RUSSELL BRAIN, Brit. M. J. **2**:605 (Sept. 17) 1938.

Brain points out that vertigo may arise as a result of disturbances of function at various levels of the nervous system. His classification includes: (1) psychogenic vertigo, (2) vertigo due to cortical disturbances, (3) vertigo of ocular origin, (4) vertigo of cerebellar origin, (5) vertigo due to lesions of the brain stem, (6) vertigo due to lesions of the eighth nerve and (7) aural vertigo. An analysis of 41 cases indicates that the average age of onset is 49 years. Brain believes that focal sepsis is the most important etiologic factor. Most patients respond well to some form of medical treatment, but surgical division of the vestibular fibers of the eighth nerve occasionally is necessary.

ECHOLS, New Orleans.

THE PUPILS IN THE DYNAMIC STATE. ALBERT MONBRUN, Rev. neurol. **69**:602, 1938.

Iridoconstriction to light is the only true visual reflex of the pupil. The other forms of iridoconstriction are associated movements. The direct reflex has a latent period of 0.2 second. After the constriction there is slight dilatation followed by slight hippus, before the final dilatation to the diameter preceding response to the light stimulus. All these phases are subject to great individual variations. Pupillary fatigue, following repeated stimulation, may disappear under the influence of emotion. The pupillary reflex is best obtained by illuminating the macular region. If it is very weak, the constriction may be observed with the corneal microscope. The consensual reflex is best observed by illuminating both eyes and then masking one eye. If the other eye is blind the pupil will dilate. In cases of hemianopia Wernicke's hemianopic reaction, when positive, indicates a lesion of one optic tract, but a negative response does not eliminate a lesion of the optic tract. The pupillary reaction to accommodation convergence is part of an associated movement. It is bilateral: during accommodation the pupil of the masked eye contracts as well as that of the exposed eye. It occurs when the object fixated is less than 40 cm. from the eye and reaches its maximum when the object is at 15 cm. Two other associated movements are Tournay's reaction or dilatation of the pupil on the side toward which one looks, and the reaction of Piltz or Westphal, or contraction of the pupil during strong voluntary occlusion of the eyelids. When the lids are suddenly opened the pupils are seen to dilate, even in a strong light. Nonvisual reflexes of the pupil are numerous. Local pain, such as that from a foreign body or corneal ulcer, produces contraction, while distant pain, a disagreeable sensation of any modality or strong emotion produces dilatation. This includes a sudden and intense sensation of light, which results in dilatation before the constrictor reflex intervenes. In addition to pain sensation provoked by pinching or cutting which is mediated by the trigeminus nerve, the iris has direct photoirritability. The iris of dead eyes or fragments of iris in Ringer-Locke solution contract to light. Photophobia and miosis associated with iritis are explained in this manner. Monbrun found that solutions of acetylcholine have no effect on the intrinsic ocular

muscles, but result in constriction of the pupil and spasm of the ciliary muscle when they are injected under the conjunctiva. Instillation of corynanthine hydrochloride has been found by Besançon and Voisin to counteract mydriasis produced by ephedrine and to produce miosis without spasm of accommodation. It is a pure sympathoplegic drug, unlike physostigmine, which produces spasm of the ciliary muscle.

LIBER, New York.

TOPOGRAPHIC SYNDROMES OF THE CENTRAL VESTIBULAR PATHWAYS IN MAN. J. A. BARRÉ, Rev. d'oto-neuro-opht. **16**:420 (June) 1938.

This article is a continuation of Barré's report to the Tenth Congrès des Sociétés d'Oto-Neuro-Ophtalmologie. The first part was published in the May 1937 issue of *Revue d'oto-neuro-ophtalmologie* (page 321).

In order to clear up misunderstandings of the terms "deficit" and "irritation," Barré defines them as follows: By deficit, as applied to a nerve pathway, is meant absence, disturbance or diminution of conduction and the disturbances resulting from it. For the vestibular apparatus, a deficit would be shown by disturbance or lack of sensation or reflex, in whole or in part, in the distribution of its components. The term irritation implies a redoubling of physiologic activity; this activity is abnormal because of its degree or duration. The phenomena of deficit and irritation may coexist in a large number of pathologic conditions. In certain other cases each may appear in a pure state. They are common to the central and the peripheral neurons. That a lesion may have a double effect is proved by the frequent observation of a case in which conduction is arrested in the peripheral neuron by a lesion that at the same time is the source of abnormal excitation of the central neuron. Certain lesions produce particularly the signs either of deficit or of irritation, so that clinical analysis may warrant an opinion concerning the nature of the lesion. An acoustic tumor, of slow development, may exist for years without producing symptoms other than unilateral deafness. Other lesions, developing more rapidly, produce early marked tinnitus, while the hearing is only slightly affected. Barré cites the vestibular disturbances observed in cases of syringobulbia and multiple sclerosis as examples of irritative syndromes. Complex syndromes are produced by lesions that involve both the vestibular apparatus and the cerebellum. Only recently has an attempt been made to analyze separately the syndromes of these two regions. Vestibular hypotonia associated with cerebellar hypotonia causes excessive nystagmus; in the test of the extended arms, however, it may happen that either one or both arms, which would be displaced horizontally in a given direction if the vestibular apparatus alone were involved, remain immobile or deviate to the opposite side if the cerebellum is also involved. The vestibular harmony has been broken by participation of the cerebellum.

The vestibular syndromes may be grouped into a few general types: complete, partial and associated and combined syndromes. The vestibular syndromes are made up of (1) subjective signs, such as sensation of vertigo or pulsion; (2) spontaneous or revealed objective signs (deviations of the head, eyes, trunk and arms or rotation around the axis), and (3) provoked objective signs (revealed by caloric, rotatory and galvanic tests). The complete vestibular syndrome is unilateral or bilateral. When bilateral, there may be predominance on one side; nystagmus or a deviation may be so accentuated on one side as more or less to mask the same element of the syndrome on the opposite side. In such a case, only instrumental tests will determine the respective value of one or the other side. Partial vestibular syndromes have been represented until recently by the partial vestibulo-ocular syndrome or the vestibulospinal syndrome. Of the partial vestibular syndromes an important example is crossed vestibular dysreflexia or areflexia, in which the causal lesion is located in a restricted segment of the central vestibular pathways, a part of the chiasm of the vestibular pathways.

In a large number of lesions involving the peripheral and bulbomesencephalic segments of the vestibular tracts one observes, besides the spontaneous or provoked reactional movements, a modification of the general bodily equilibrium. In

lesions situated in the temporal, parietal and frontal poles, disturbance of the axial equilibrium of the body is accentuated. Barré believes that the peripheromesencephalic vestibular apparatus is integrated into the general apparatus of equilibration and constitutes a reflex mechanism, the sensorial and motor pathways of which are articulated in the bulb and peduncle. Above it lies an apparatus for automatic regulation, reduced to a small number of pathways that are assembled in the red nucleus, and perhaps a little higher. The hemispheric cortex probably plays an important role in the perception of the sensations of equilibrium or disequilibrium; it is the conscious and voluntary mechanism, disturbance of which is so often shown by retrolateropulsions or other deviations of the axis of the body, or even by falling. Ascending pathways from the otoliths, canals and posterior columns, and perhaps other pathways, are dissociated and distributed to various cortical areas on arriving at the subthalamic or retrothalamic region. That association pathways from these areas connect with the frontal or prefrontal cortex is probable. It is not astonishing that when the prefrontal area is affected directly or indirectly it may be the point of passage or departure of a disturbance in general equilibration. A special disturbance of equilibration will be created when the representation of space is altered; a different disturbance will occur when the faculty of attention is diminished.

A comparison of the clinical data with the anatomic arrangement is relatively easily made in cases of lesions of the vestibular nerve. This is more difficult with lesions of the bulb. The studies of Lorente de Nó indicate a greater complexity of the intrabulbar reflex pathways than had previously been supposed. Clinical observations indicate a precise anatomic localization for the syndrome of crossed dysreflexia in a lesion of one half of the pons near the midline and slightly above the nucleus of the sixth nerve. This has as yet no demonstrable anatomicoclinical support. In the peduncular region superposition of the clinical and the anatomic descriptions is again easy. The schema of van Gehuchten and Winkler permits a clear understanding of the various particulars of the vestibular syndromes of lesions of the peduncular tegmen, whether they are situated below, at or a little above the red nucleus. Lesions of the hypothalamic cross roads produce diverse disturbances, but the number of known cases of vestibular syndromes referable to this region is not sufficient to determine whether they are explicable by its anatomic structure. In the regions located still higher the vestibular pathways have scarcely been mapped.

Dusser de Barenne and de Kleyn have shown that in rabbits after the ablation of one cerebral hemisphere the two vestibular mechanisms remain equally excitable and that the quick component of nystagmus, which is toward the side of operation, may be much stronger than that on the other side, whatever the method used to provoke it. The same phenomenon has been observed in man, either as simple predominance of the direction of nystagmus or in a pure and complete state. It is interesting that a minimal, or even fugacious, lesion in man can produce the same syndrome as ablation of an entire hemisphere in a rabbit. Muskens' experiments on animals led him to postulate "supravestibular pathways," which arrive at the pallidum via the posterior commissure. Serious doubts have been expressed about Muskens' interpretations, but he demonstrated that various *muovements de manège* and axial rotation can be produced by operation on the highest part of the peduncles. The tendency to axial rotation observed in certain cases in man, associated with a homolateral or contralateral pulsion of the body, generally without nystagmus and deviation of the arms, is a new and important fact and directs attention to the anterior peduncular region. The experiments of Foerster, Spiegel, de Kleyn and Versteegh and Benjamin have yielded interesting data on the physiologic reactions of the region surrounding the interparietal sulcus. This is the only point at which excitation can produce the sensation of vertigo in man. It is probable that the mechanisms of the quick component of nystagmus and of the optokinetic reflex are in connection with this sulcus; it is also probable that fibers from the utricular otolith end there, while those from the saccular otolith go to the auditory center in the temporal lobe. Parietal lesions occupy the first rank among corticosubcortical lesions that may disturb general equilibration. DENNIS, San Diego, Calif.

CLINICAL STUDY OF VESTIBULAR DISHARMONY. A. CHARBONNEL, Rev. d'oto-neuro-opht. **16**:513 (Oct.) 1938.

A harmonicus vestibular syndrome is characterized by the presence of slow reactional movements, all in the same direction: nystagmus, deviation of the body and deviation of the extended arms. The semeiologic significance of a harmonious vestibular syndrome is that of a peripheral lesion on the side toward which the movements are directed. When there is a difference in direction of two or more of the slow reactional movements, there is then a disharmonious vestibular syndrome (Barré). All observers are not agreed on the significance of the disharmonious syndrome. Barré regarded it as a cerebellar sign, since in all his cases cerebellar lesions were discovered at operation or at autopsy. The elements of the syndrome were due to involvement of the vestibular tracts, but a cerebellar disturbance was necessary to explain their grouping. Ramadier and Caussé expressed the belief that disharmony of the vestibular syndrome was due solely to a central disturbance of the vestibular pathways. Charbonnel, after a study of 20 cases, expressed preference for the theory of Barré.

He now reports the results of a study of 5 additional cases, including 1 of cerebellar tumor, 3 of multiple sclerosis and 1 of an infectious process in the posterior fossa. The condition in all the cases was characterized by constancy of the vestibular manifestations; no transformation or reversal of the provoked nystagmus by altering the position of the head; slight vertigo, occurring both spontaneously and after testing, and unequal distinctness of the various elements of the syndrome. The possible combinations of the elements of vestibular disharmony are multiple. Whatever its form, it indicates abnormality in the central part of the vestibular tract. This applies whether the disharmony occurs spontaneously or after instrumental tests of the labyrinth. Caloric areflexia, together with normal or rotatory excitability, is not disharmony, although such dissociation may occur in cases of lesion of the fourth ventricle; it occurs likewise with peripheral lesions, such as syphilitic neuritis of the eighth nerve or tumor of the nervus acusticus in its early stages. Vestibular disharmony practically never occurs in cases of peripheral lesions. A disharmonious vestibular syndrome, arising during the course of otitis, indicates the possibility of a central complication and requires further investigation such as lumbar puncture. While alteration of the central vestibular tracts alone gives rise to vestibular disharmony, it is also true in Charbonnel's experience that it is always associated with a disturbance of the cerebellar apparatus, usually the vermis. The chief value of the sign of vestibular disharmony is that it permits differentiation between a central and a peripheral lesion and that it is found only in disturbances situated in the posterior fossa: tumor of the cerebellum, the fourth ventricle or the cerebellopontile angle; abscess; infectious processes involving the brain stem, and occlusion of the posterior inferior cerebellar artery.

DENNIS, San Diego, Calif.

FAMILIAL NEUROTROPIC SYPHILIS: ARGYLL'S SIGN IN THREE MEMBERS OF THE SAME FAMILY. RISER, BECQ and COUADOU, Rev. d'oto-neuro-opht. **16**:553 (Oct.) 1938.

In 1932 85 homes were studied in which one of the partners was affected with syphillis of the nervous system. In a large proportion of cases the other partner presented signs of neuraxitis or of isolated syphilitic meningitis. An illustrative case was that of a man aged 49, who had contracted syphilis in 1914 and had been carefully treated for six years. In 1921 he married a woman in perfect health; two boys were born of the union. In 1923 clinical and blood examinations gave normal results but the spinal fluid contained 0.4 Gm. of albumin per hundred cubic centimeters and 6 lymphocytes per cubic millimeter; the Bordet-Wassermann and benzoin tests gave negative results. In 1928 examination revealed loss of the achilles reflex and an Argyll Robertson sign in both eyes; the Bordet-Wassermann tests of the spinal fluid gave negative results, and the spinal fluid still contained

albumin and lymphocytes. Four annual series of treatment with mercuric cyanide were instituted.

Thorough examination of the wife in 1921 revealed that she was entirely normal. In 1928 she showed a punctiform pupil of the right eye and a typical Argyll Robertson sign. There were no symptoms of neuraxitis. The Bordet-Wassermann and benzoin tests of the spinal fluid gave negative results; the fluid contained 0.8 Gm. of albumin.

The elder of the boys was normal at birth, and the Bordet-Wassermann test of the blood gave negative results. At the age of 6 years he presented Argyll Robertson pupils, associated with anisocoria and miosis in the right eye. The spinal fluid contained albumin and 5 cells, and the Bordet-Wassermann and benzoin tests gave positive results. The second son was healthy, and the spinal fluid was normal.

This observation does not decide the question of the duality of the syphilitic virus. Chance and coincidence do not explain the occurrence of familial syphilis of the nervous system. Probably there are affinites of certain microbian stocks, but the belief in the existence of two kinds of syphilis, a neurotropic and a dermotropic, is not authorized.

DENNIS, San Diego, Calif.

Cerebellum and Brain Stem

SYNDROME CHARACTERIZED BY PROGRESSIVE CEREBELLAR ATAXIA WITH FEEBLEMINDEDNESS. M. MAERE and G. MUYLE, J. belge de neurol. et de psychiat. **38**:96 (Feb.) 1938.

Maere and Muyle report the cases of 2 young Polish Jews, a brother and sister, who presented early in life a syndrome consisting of progressive ataxia, skeletal anomalies and arrested mental development. They showed generalized hypotonia, dysmetria, asynergy and dysdiadokokinesia, with difficulty in walking. Both showed nystagmus and incoordination of ocular movements. The brother had certain skeletal changes—scoliosis, brachydactyly and reduction in the size of the cranium—and the sister showed precocious sexual development. No other members of the family had similar difficulties. The authors compare the findings with those observed in Friedreich's ataxia. They believe that the two conditions are different.

DE JONG, Ann Arbor, Mich.

EXPERIMENTAL PRODUCTION OF CIRCULATORY DISTURBANCES IN THE CEREBELLAR BLOOD VESSELS IN RABBITS. C. O. NYLEN, Confinia neurol. **1**:157, 1938.

Nylen carried out experiments in an attempt to ascertain the nature of the symptoms which follow interference with the blood supply to the mesencephalon and metencephalon and to the labyrinth. He found that constant interruption of the blood supply to certain areas in the mesencephalon and metencephalon gives rise to symptoms similar to those in Ménière's disease. There was no involvement of the labyrinths in any of the experiments. Nylen believes that the symptoms are due to the resulting ischemic degeneration in the parts of the brain which contain centers of importance in the maintenance of balance.

DE JONG, Ann Arbor, Mich.

Experimental Pathology

JAPANESE B ENCEPHALITIS VIRUS: ITS DIFFERENTIATION FROM ST. LOUIS ENCEPHALITIS VIRUS AND RELATIONSHIP TO LOUPING ILL VIRUS. L. T. WEBSTER, J. Exper. Med. **67**:609 (April) 1938.

Webster states that poliomyelitis, Japanese B encephalitis, Australian X disease and St. Louis encephalitis have features in common but are distinguishable by

laboratory tests. Outbreaks of each are frequent and limited chiefly to hot weather. Each may be recognized by testing serums of convalescent patients for specific neutralizing properties against one of these virus agents or by obtaining virus from the cerebral tissue in cases of fatal outcome and testing its virulence for mice, monkeys and sheep and its neutralization in specific antiserums. The sheep virus is probably infectious for man. Louping ill virus has been related to the virus associated with X disease of children in Australia and now has proved similar to the newly discovered virus of Japanese B encephalitis. Laboratory tests on susceptible animals indicate clearly that the most vulnerable port for the experimental introduction of these viruses is the nasal mucosa; this is the route of choice in mice for the St. Louis virus; in mice, monkeys and sheep for the viruses of Japanese B encephalitis and louping ill, and in monkeys for the poliomyelitis virus. There is also evidence that spontaneous infection with louping ill may occur both in man and in mice through the nasal mucosa. Contact experiments to induce spontaneous transfer of infection with St. Louis and Japanese B encephalitis and poliomyelitis among susceptible laboratory animals have failed, however, and it is difficult or impossible to detect the virus in the upper part of the respiratory tract of the diseased animal. Subcutaneous injections of Japanese B and louping ill viruses in mice and of poliomyelitis virus in monkeys and possibly in man may also induce disease. Reports state that in nature infection of sheep with the louping ill virus takes place subcutaneously by the bite of an insect. Experiments to detect virus in the blood of patients after natural or experimental infection are either positive for brief periods only (louping ill and Japanese B viruses) or completely negative (poliomyelitis and St. Louis viruses). Hence, there is evidence for and against both the upper respiratory and the subcutaneous route of transmission of these infections, and the question remains perplexing.

EDITOR'S ABSTRACT.

EXPERIMENTAL INVESTIGATION INTO THE CAUSE OF PARALYSIS FOLLOWING SPINAL ANAESTHESIA. A. D. MACDONALD and K. H. WATKINS, Brit. J. Surg. **25**:879 (April) 1938.

Macdonald and Watkins studied the effects of intrathecal injections of spinal anesthetic solutions and the various constituents of these solutions in 150 cats. The study revealed: 1. Certain cocaine substitutes, in concentrations commonly employed clinically, though in relatively larger doses, may produce lasting paralysis comparable to lesions of the cauda equina. 2. Improvement in these cases is usually apparent in about six weeks, but cure may be incomplete in six months. 3. The common constituents of the solution other than the local anesthetic drug do not of themselves produce lasting paralysis in the concentrations in which they are normally employed.

EDITOR'S ABSTRACT.

Society Transactions

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

JAMES M. STANTON, M.D., *in the Chair*

Regular Meeting, Jan. 19, 1939

EVALUATION OF PHARMACOLOGIC SHOCK TREATMENT. DRS. L. S. LIPSCHUTZ AND R. W. CAVELL, Eloise, Mich.

Since January 1937 over 150 patients have been treated with insulin and metrazol at the Eloise Hospital. Of these, 82 (35 with insulin and 47 with metrazol) were in the female division. Because shock therapy remains largely an empiric method, an attempt was made to carry on these treatments under conditions in which several factors believed to be of therapeutic potency could be evaluated. Accordingly, the patients given insulin were treated in groups of 6 under standardized conditions: In one group hypoglycemia with coma was induced; in a second, hypoglycemia was induced without proceeding to the level of coma; in a third, hypoglycemia, coma and intensive resocialization activities were employed; in a fourth, hypoglycemia was induced without coma and intensive resocialization activities were used, and in a fifth, injections of physiologic solution of sodium chloride instead of insulin plus intensive resocialization activities were employed.

Tabulation of the therapeutic results indicated a preponderance of social recoveries among those treated with a combination of hypoglycemia carried to the level of coma and intensive resocialization activities. Less satisfactory results occurred when hypoglycemia was carried to the level of coma, but intensive resocialization activities were not employed, and results were least satisfactory when physiologic solution of sodium chloride was used in place of insulin. Even in the last group, however, moderate degrees of improvement were noted in cases of long-standing schizophrenia, and although the number of patients treated in the various groups was not considered large enough to be of statistical validity, it was believed that psychologic factors, such as increased attention to the patient, an optimistic attitude on the part of the personnel and, possibly, improved nutrition, due to greater attention to food intake, were factors of therapeutic potency.

No correlation could be established between the attitude of the patient toward treatment, that is, whether apathetic, apprehensive, resistive or submissive, and the therapeutic response. A similar lack of correlation existed as far as the hereditary background of the patient was concerned. The average duration of the psychosis in this group of female patients with chronic schizophrenia was approximately four years, the range being from one to ten years. Eleven patients were classified as socially recovered or markedly improved, and 15 as moderately improved, and the condition of 9 was essentially unchanged. When these results were compared with a control group of 100 schizophrenic patients admitted during 1936, it was found that the number of socially recovered and markedly improved patients in the latter group was 20 per cent, as compared with 35 per cent in the group treated with insulin.

The 47 patients treated with metrazol included 38 patients with schizophrenia and 9 with manic-depressive psychoses, depressed phase, or with involutional melancholia. Only 16 per cent of the schizophrenic group improved to the level of social recovery or marked improvement; these results were disappointing. Among the patients with affective psychoses, the therapeutic results were striking, 6 of 9 persons exhibiting satisfactory remissions.

It was found that the therapeutic response could be correlated definitely with the attitude of the patient toward treatment, there being a preponderance of apprehensive and resistive attitudes among those showing the most improvement, and it was suggested that fear of treatment might play a part in the therapeutic result. As with the insulin-treated group, no correlation could be established between hereditary background and therapeutic response.

A depressed patient who expressed much guilt and need for punishment later made an unsuccessful attempt at suicide, which was followed by complete remission persisting for four years. It was thought that the unsuccessful attempt satisfied the need for punishment and therefore acted to relieve the feelings of guilt responsible for the psychosis. On this basis, several patients with manic-depressive psychoses, depressed phase, and involutional melancholia who expressed many feelings of guilt and spontaneous demands for punishment were treated with metrazol. The explanation was offered that the clinical improvement noted occurred because the metrazol treatment was interpreted at the psychologic level as punishment, which tended similarly to relieve the feelings of guilt. The rate of improvement of 66 per cent for the patients with affective psychoses treated with metrazol was compared with a rate of 14 per cent for a group of 15 patients treated with estrogenic substitution therapy.

No fatalities in shock treatment were reported. The complications noted with metrazol therapy were fractures in several cases and transient electrocardiographic changes. With insulin treatment, several cases of prolonged coma and 1 case of acute pulmonary edema were noted. After the dose of insulin producing coma had been reached and established for some time, a type of conditioning developed by which coma could be repeated with smaller doses. The percentage of reduction in the dose possible in some cases was as high as 50 per cent. Utilization of this fact and the arbitrary limitation of the entire period of hypoglycemia to not more than five hours helped to prevent the occurrence of irreversible changes.

DISCUSSION

DR. FREDERIC SCHREIBER: There is a certain comparability between the reaction in cases of shock treatment and that in cases of traumatic injuries to the brain as observed by the neurosurgeon. First, as to the selection of cases: Although the conditions in the cases presented tonight were of somewhat longer duration, the ideal case seems to be one in which the disease has been present for less than a year. I do not know much about schizophrenia, but it is my impression that it is a disease having to do with the layers of the patient's experience. I believe that experiences are acquired in layers. In the case of the schizophrenic person something has gone wrong with the last layer of his experience, and the benefit from treatment, I believe, is due to the fact that the last layer of experience has been removed by actual destruction of the cortex of the frontal lobe.

To secure a favorable result after insulin or metrazol therapy there must be retrograde amnesia. I see such results in work among patients with trauma, especially boxers and musicians who have acquired certain conditioned responses. Foster Kennedy reported a case which demonstrates this point. The patient, with an injury of the left frontal lobe, was a trained artist. When she regained consciousness, he asked her to copy a picture on the wall, which was a profile of Alexander Hamilton. She drew a circle with four dots in it to represent the eyes, nose and mouth, the kind of thing she would have drawn at the age of 6. Then she cried because she knew there was something wrong with the picture. Dr. Kennedy asked his patient to copy the same picture at intervals of every few weeks for a period of eight months or so; gradual improvement was shown with each drawing, until at the end of the time she again revealed herself as a gifted artist.

During the last few years I have seen improvement in cases of schizophrenia with the following methods of treatment, it being necessary in all to carry the patient to the point of coma or convulsions, with resulting retrograde amnesia: First, prolonged coma was induced with barbiturates; then, carbon dioxide was given to the point of apnea; then, insulin and metrazol were employed, both being used to the point of coma and convulsions. I have also seen improvement in such cases as those reported by Watts and Freeman in which tissue of the frontal lobe was purposely destroyed. Dr. T. K. Gruber has reported that several patients at the Eloise Hospital improved after severe typhoid fever, with high temperatures and delirium. All these treatments have one thing in common, the production of cerebral anoxia. Post mortem the brains all show anoxic degenerative lesions. Cerebral anoxia, however induced, first affects the cortex of the frontal lobe, and permanent changes, if present, will be seen in the cortical cells of this region. It is my impression that all these methods of treatment consist merely of repeated anoxic insults, which strip a last layer of experience from the schizophrenic patient and take him back to a time before the onset of his mental change.

From the standpoint of safety and economy, I suggest that nitrogen monoxide asphyxia be employed repeatedly in treatment of a series of schizophrenic patients. Such asphyxia would have to be carried to to the point of coma and convulsions. There is no doubt that such a method would have some of the hazards of all the other methods which have been employed. The purpose of using nitrogen monoxide asphyxia would be to destroy a part of the cortex of the frontal lobe by means of the mechanism of cerebral anoxia.

I believe that the efficacy of all the so-called shock methods depends on partial destruction of the frontal cortex, with the attendant change in character and retrograde amnesia. It is important that the psychiatrist take the patient by the hand after such an ordeal and teach him to meet his new experiences in a more normal manner.

DR. THOMAS J. HELDT: In the Henry Ford clinic I have always emphasized the psychotherapeutic side of the treatment. It is not merely the insulin; it is not merely the coma, or even the cerebral anoxia; it is the person receiving the treatment. The patient may need to escape punishment or to receive it in order to clear away the masquerade, as Dr. Schreiber described. However, there must be something with an orientation value, and I believe the physician or nurse who is with the patient is a highly important factor. Objectification must be present not merely to the physician, but to the patient.

DR. L. S. LIPSCHUTZ, Eloise, Mich.: I am not prepared to accept a purely organic view of schizophrenia, and I shall cite an experience. E. J. had been a patient in the hospital for nine years. She was destructive, and self mutilative and had many bizarre delusions and hallucinatory trends. She improved to the point where one could hold a conversation with her. She has a husband who limps, and physically is not particularly attractive, and they have five small children. After much persuasion, they were induced to visit her, although they had long given up the habit. This was done in the hope that it might stimulate her interest. She had apparently been well. When her husband and the five children walked in, she took one look at her husband and said: "Are you here again, you cripple?" and almost immediately reverted to her former status. I don't see how that can be explained on the basis of an organic process.

DEMONSTRATION OF MENTAL MECHANISMS BY HYPNOSIS. DR. MILTON H. ERICKSON, Eloise, Mich.

After general introductory remarks on the special advantages of hypnosis as a means of demonstrating the mechanisms and dynamics of behavior, I introduced 3 normal subjects to the audience and conversed casually with them to demonstrate their ordinary behavior. This was followed by the rapid hypnotizing of all 3 subjects, with demonstration of some of the more common hypnotic phenomena,

particularly ideomotor action, catalepsy, rapport and, finally, the somnambulistic hypnotic trance in which the subjects give an outward appearance of being awake and in full contact with their surroundings and yet are actually completely out of contact with their surroundings except as instructed by the hypnotist. Then followed a series of demonstrations directed to the clarification of various psychic dynamisms.

Subject 1, on reaching the somnambulistic state and opening his eyes, was found to be oriented as if he were in my office, rather than in a lecture hall before an audience. This orientation on the part of the subject was found to be entirely valid, and every response he made, direct or indirect, disclosed him to be acting entirely as if he were actually in my office. This manifestation was discussed in detail, emphasis being placed on the hypnotized subject's ability to exclude, or to fail to respond to, external stimuli and to react to internal stimuli as if they derived from the outside; a parallel was drawn with the reality of the delusional beliefs of psychotic patients.

Subject 2 was then placed in rapport with Dr. R. W. Cavell, and a casual conversation followed, after which I made a long series of suggestions to the subject to the effect that she was acquiring a retroactive amnesia extending to the tenth year of her life. In this manner it was possible to induce this young woman to "regress" in the patterns of her behavior and to react as if she were 10 years of age, giving the responses characteristic of a child and showing the emotional reactions, the general social patterns and the juvenile attitudes characteristic of that age. The subject in the mental state of 10 years was then interviewed by Dr. H. Reye, who questioned her extensively, eliciting replies in accord with the understanding of a child of 10.

This demonstration was discussed with emphasis on the necessity of a time-taking procedure of suggestion as a measure of permitting the subject, who is receiving such suggestions, to acquire the "mental set" by means of which there can be reestablished the levels of mentation characteristic of any suggested age without interference from subsequently acquired experiences. A parallel was drawn with the forms of regression encountered psychiatrically.

Subject 3 was then employed to demonstrate, while in the somnambulistic state, the phenomenon of negative hallucination. Dr. Cavell was pointed out, and the subject was told that shortly he would leave and that she would not see him again. After these suggestions had been given effectively, innumerable attempts were made by Dr. Cavell to establish either a positive or a negative contact with her, but the subject manifested neither avoidance of nor response to him. So far as could be determined by indirect as well as direct measures, the subject remained totally unable to make any form of response to Dr. Cavell. This was discussed, and a parallel was drawn with various forms of denial of reality observed in psychotic patients.

Hypnotic suggestions were given to subject 1 to the effect that there would appear on the floor a large crystal in which he was to see a crystal image of recent events. The subject accepted these suggestions and had a remarkably complete visual image of the lecture room as it had been during the earlier part of the evening; extensive questioning disclosed that the experience for the subject was exceedingly realistic. Discussion was offered, and parallels were drawn with the processes of reliving as it develops in psychotherapeutic measures.

Subject 3, still in the somnambulistic trance, was given a series of suggestions directed to the evocation of the phenomenon termed "resistance." To this end the subject was instructed to be entirely courteous and compliant toward Dr. S. H. Ruskin in every detail; yet at every opportunity the subject was to avoid, escape, evade, resent and resist every casual request or conversational remark made. After a brief pause, the subject was awakened and a casual conversation initiated, leading to the introduction of the subject to Dr. Ruskin. Then followed a general conversation, in which the subject missed no opportunity, however direct or indirect, to oppose Dr. Ruskin in every conceivable way, yet maintaining an attitude of impeccable courtesy. An attempt was made by Dr. Ruskin to have

the subject take another seat, and every request and insistence on his part was countered effectively by courteous resistance; when he finally made it impossible for the subject to avoid compliance, the latter yielded, but moved the chair to a new position, thereby subtly nullifying the compliance. This behavior was discussed in detail in relation to the problems represented by both conscious and unconscious resistance shown by patients.

Subject 2, in the deep trance, was instructed that after awakening she was to recall a trip made by the hypnotist to Detroit, in an effort to visit a certain hospital, and the losing of his way. The subject was given a false address for this well known hospital and was told to insist, argumentatively, when awake, that this false address was the only correct one.

After awakening, subject 2 obeyed instructions fully and became involved in arguments with the members of the audience as to the location of the specified hospital. Innumerable items of proof were advanced by the subject to confirm the false address, and I discussed in general the fixity of the subject's beliefs and the general imperviousness to any reasoning approach to her delusional ideas. A parallel was drawn between this behavior and the general attitude taken by the psychotic patient when a reasoning approach is made to any form of abnormal ideation.

To subject 3 there was then suggested, in the deep trance state, a phobia for cats, and a long series of suggestions was given, building up in the subject an intense fear, dislike and abhorrence of cats and anything connected with them. The subject was told that this fear would persist even after awakening, but that it would be concealed, denied and repressed from all conscious awareness. After this complex has been thoroughly implanted, the subject was allowed to awaken. Dr. Cavell took a seat beside the subject and by slow degrees led up to the topic of people's interests in pets. When this conversation had been well established, the subject began manifesting intense and uncontrollable abhorrence of and disgust for people who had any interest in animals, particularly cats, and numerous instances were cited by the subject in which persons who liked cats were found to be undesirable or abhorrent. Finally, the conversation disclosed that Dr. Cavell owned a cat, whereon the subject showed a marked distaste for the proximity of her chair to Dr. Cavell, and recourse was had to various subterfuges on her part to effect a change to another seat. Dr. Reye then approached the subject to ask questions about cats, with the result that the subject became increasingly tense and emotional and unable to discuss cats without expressing intense, unreasoning and irrational hostility toward them. Finally, when questioned as to the duration of this feeling of hatred toward cats, the subject gave a long story about always having hated and abhorred cats. When all the classic manifestations of an acute phobia had been manifested clearly and unmistakably, the subject was rehypnotized and the phobia removed completely by psychotherapeutic suggestions and the giving of insight.

After this, subject 3 was rehypnotized, and a second complex was implanted in which the subject was told that, purely by accident, through a state of absent-mindedness, she had seriously offended subject 1, with whom a friendly feeling had always existed. The subject was told that this insult now belonged to the past, that there was nothing that could be done about it and that it might just as well be completely repressed and forgotten.

After this, subject 3 was awakened, and, by manipulation of the situation, subjects 3 and 1 engaged in a casual conversation. During the course of this, subject 3 resorted to every conceivable misunderstanding of subject 1's remarks to offer an apology. Overcompensatory behavior and inexplicable embarrassments were demonstrated by the subject in a clear fashion. Many of the remarks made by subject 3 carried a double meaning easily apparent to the audience, but which bore only a simple conscious significance to the subject. In elaboration of the demonstration, I discussed the significance and effects of repressed material on ordinary behavior.

Subject 3 was again hypnotized; the previous complex was removed, and suggestions of an intense desire to smoke were given. At the same time the subject was instructed to want to avoid smoking, to hate smoking and yet to feel bound by an uncontrollable desire to smoke, a smoking compulsion being thereby effected. On awakening, the subject manifested marked restlessness, made several remarks about my smoking, commented that I seemed to have matches, and remarked that I had sometimes offered people cigarets; when one was offered to her, it was rejected with a statement that a cigaret of a special brand was desired. Since a package of this special brand was found in the audience, a cigaret was offered to the subject, who took it unwillingly and refused to smoke unless some one else joined in the act. After much dilatory activity and ineffective efforts to light the cigaret, the subject finally began to smoke in an easily recognizable compulsive fashion, becoming harshly critical of the cigaret and of the general situation, obviously not enjoying the cigaret and yet feeling compelled to smoke. Every effort made on the part of members of the audience to induce discontinuance of the smoking met with firm resistance, despite the subject's repeated insistence that she had no desire to smoke and despite her ready desire to get rid of the cigaret, the subject finally began to smoke in an easily recognizable compulsive obsessive forms of behavior.

After this, I gave a general review of the various demonstrations and drew parallels between psychoneurotic behavior, psychotic behavior and normal behavior and the various types of behavior manifested by normal hypnotic subjects, closing my remarks with emphasis on the value of hypnosis as an instrument for the teaching of the dynamics of behavior and as a means of creating within the laboratory various types of behavior which could then be subjected to critical laboratory analysis.

CHICAGO NEUROLOGICAL SOCIETY

VICTOR E. GONDA, M.D., *President, in the Chair*

Regular Meeting, Feb. 16, 1939

ACUTE ENCEPHALOMYELITIS: EQUINE OR AVIAN? DR. M. A. FOSTER, Madison, Wis. (by invitation).

Equine encephalomyelitis has swept the plains of central Europe in recurrent epizootic form since the early nineteenth century. Its tendency to become enzootic in the region of Borna, Saxony, in 1883 to 1900, resulted in the careful studies by Zwick, Meissner and others on its etiology. The disease has been known in the Middle West since 1847. Since the description by Meyer and his associates of the San Joaquin valley epizootic in 1930 (*Science* **74**:227 [Aug. 28] 1931), the disease has been recognized throughout the United States.

The etiologic agent has been shown to be a virus (size, 200 millimicrons), which is thermolabile and sensitive to sunlight. There have been isolated (the Eastern and Western United States strains, four Russian strains and the Zwick, the Venezuelan and several South African strains, some of which are closely related. Practically all the common laboratory and farm animals, including birds, have been proved to be susceptible, and the virus has been transmitted under experimental conditions by the Aedes mosquito.

The epizootic form shows a seasonal recurrence, the outbreak beginning in June or July and terminating with the first frost. Animals of all ages are susceptible, and the symptoms show a wide variation. The acute forms may have a sudden onset with fever, followed by loss of ability to coordinate, disturbances in gait, hyperesthesia, paralysis of the muscles of the tongue and pharynx with dehydration, coma and death in thirty-six hours. Other animals may show little more than slight anorexia or irritability.

The first cases in man were reported by Meyer (*Ann. Int. Med.* **6**:645 [Nov.] 1932); the disease involved men exposed by direct contact and terminated fatally in all cases. In 1938 scattered cases were reported in California, Wisconsin and Minnesota, while an epidemic occurred concurrently in New England among pigeons and pheasants as well as horses.

Two cases are reported in which there was recovery. The chief clinical findings, aside from certain residuals, were the high protein content and low cell counts of the spinal fluid, which persisted for six months.

It is pointed out that migratory birds are susceptible to this disease and that the Western United States strain extends through most of the Argentine, Brazil and Chile, where many of these birds winter.

PINEALOMA OF DIFFUSE EPENDYMAL ORIGIN. DR. R. P. MACKAY.

This paper will appear in a later issue of the ARCHIVES.

THE FASCICULUS SOLITARIUS AND ITS NUCLEUS IN THE HUMAN BRAIN. R. M. STRONG.

Descriptions in textbooks of the fasciculus solitarius and its nucleus are based primarily on work done with small mammals. Parts of these structures are easily seen in ordinary Weigert-Pal preparations. Large rostral and caudal portions are lost in a forest of myelinated fibers.

I began work on the subject about fifteen years ago. A graduate student, Dr. E. G. Cada, was assigned the problem of making plaster of paris and graphic reconstructions of such portions as could be discerned in an especially fine series of sections of the brain stem (Kultschitsky-Weigert stain).

I completed the study of more rostral and caudal portions, using many other preparations. These included sections cut at various angles and sections of more than 50 human embryos.

CONSTITUTIONAL DIFFERENCES BETWEEN DETERIORATED AND NONDETERIORATED PATIENTS WITH EPILEPSY: IV. DACTYLOGRAPHIC STUDIES. DRS. HARRY A. PASKIND and (by invitation) MEYER BROWN.

To determine whether there are constitutional or inborn differences between the mentally deteriorated patient with epilepsy and the nondeteriorated epileptic patient, a study was made of the digital dactylographic patterns (finger prints) of 146 deteriorated and 115 nondeteriorated patients. The digital dactylographic patterns have been shown to be formed during the third or fourth month of fetal life and to remain unchanged thereafter during the life of their possessor. Interesting and statistically significant differences were found between the two groups of patients. Arch patterns were found to be more frequent among the finger prints of institutional deteriorated patients, whereas the whorl type of pattern was more common in the finger prints of nondeteriorated patients. Radial patterns (radial loops, radial whorls and radial double loops taken together) were encountered more often in the nonpsychotic patients. The mean quantitative value of the patterns was significantly greater in the nondeteriorated subjects. Anomalies in the ridges of the finger prints were found in a significantly greater proportion of deteriorated than of nondeteriorated patients.

Book Reviews

Manual of Psychiatry and Mental Hygiene. By Aaron J. Rosanoff, M.D. Seventh Edition. Price $7.50. Pp. 1,091, with 87 illustrations. New York: John Wiley & Sons, Inc., 1938.

For many years psychiatrists have complained that Kraepelin has dominated psychiatric thinking too much with his rigid nosologic ideas; yet most textbooks have reflected adherence to the Kraepelinian system of classification. Rosanoff has written a textbook which is refreshingly different. The monograph reflects to a large extent the author's personal bias and his special interests, which give it a flavor of its own, with many virtues and, at the same time, certain defects. There is a thorough presentation of the biologic, genetic and social points of view, which are helpful to the reader who wishes to orient himself with the current trends of thought in psychiatry. The profusion of references and the original quotations from various authors, as well as the inclusion of current material from newspapers and personal impressions, such as Tunney's description of "punch drunk," and the author's personal genetic investigations, make the volume more a reference than a textbook. The volume follows the continental manner of dividing the material into general and special psychiatry. In the presentation of the material in general psychiatry, stress is placed on purely biologic phenomena. Here, the author takes up the neuroses and describes many syndromes. Thus, with the hysterical syndrome he describes such vague entities as the nomadic and the parasitic syndrome. It is a question whether such syndromes can be considered well defined clinical entities. Treatment of the neuroses is sketchy.

The second part of the book, dealing with special psychoses, is valuable. One is startled not to find the classic chapter on dementia praecox; instead, one finds a chapter on disorders of sexuality, which includes some of the clinical pictures associated with schizophrenia. This is a daring innovation and commits the author to the point of view that schizophrenia is essentially a disorder the center of which lies in a disturbance in the psychosexual field. Rosanoff points out, however, that many of the so-called schizophrenic psychoses belong in other groups, and he is justified in the crystallization of certain homogeneous entities. It is somewhat annoying to find epilepsy grouped under cerebral birth traumas. The chapter on cerebral arteriosclerosis is not as full clinically as one would expect in view of its importance in institutional practice. There is an excellent presentation of the symptomatic psychoses, especially the toxic psychoses, which are closely tied with recent discoveries in metabolism and other branches of internal medicine. Thus the close relation of medicine to psychiatry is emphasized. It is gratifying to find a chapter on borderline states. On the whole, the author has written a manual of psychiatry which is original and is a contribution to the literature of psychiatry.